QUALITY OF LIFE AMONG WOMEN WITH RADIATION-INDUCED DERMATITIS OF THE BREAST

by

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ABSTRACT

Primary breast carcinoma is the most common type of cancer among women and radiodermatitis a frequent complication of treatment. The study aims were to examine the feasibility of measurements of radiodermatitis and gain a better understanding of quality of life (QOL) among 40 women with grade 0-III breast carcinoma receiving radiotherapy at a community cancer center.

Study design feasibility, clinician-measured breast length, and multiple assessments of breast radiodermatitis were explored in a pilot study. Maximum radiodermatitis score significantly correlated with breast length (p =.04), and with the following breast areas: upper inner quadrant (p=.04), upper lateral quadrant (p=.02), and lower lateral quadrant (p=.02), inframammary fold (p=.001). Clinician-measured breast lengths and participant-reported bra cup sizes were discordant estimates of breast size.

Change in skin-related and global QOL between baseline and at week 5 on radiotherapy was measured using the Dermatology Life Quality Index (DLQI) and the Quality of Life Instrument-Breast Cancer Patient Version. The relationship between, and factors associated with, skin-related and global QOL were examined. In general, skin-related and global QOL were highly correlated. Skin-related QOL changed profoundly (M=.40, SD=1.19; versus M=3.88, SD=3.55, t(-6.32), p<.001) while global QOL did not change (M=296.90, SD=74.18; versus M=292.55, SD=72.23, t(60), p=.55) between baseline and five weeks on radiotherapy.

We initiated the validation of the DLQI when used to measure skin-related QOL in breast radiodermatitis. Thirty-one (78%) participants provided narrative feedback on how the experience represented by each DLQI item impacted her life. Agreement between DLQI ratings and coded narratives ranged from 71% to 98%. Aside from work and study, the DLQI subscales demonstrated good internal consistency, $\alpha = .84$.

Content analysis was implemented to describe 28 participants' narrative response to an open-ended question about the most important DLQI item. Analysis of 60 narratives led to the identification of six themes: perspectives on having radiodermatitis, sensations caused by radiodermatitis, knowledge and preparation for radiotherapy, prevention of radiodermatitis, emotions induced by skin changes, and physical appearance of the breast skin.

Results suggest radiodermatitis has a significant impact on skin-related QOL; breast length measurements and multiple assessments of radiodermatitis may improve breast cancer research in this area.

This dissertation is dedicated to the women who shared their

perceptions, generously donated their time and effort,

and allowed a glimpse into their lives.

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LIST OF ABBREVIATIONS

ANOVA	Analysis of Variance
COH-QOL-Breast	(City of Hope) Quality of Life-Breast Cancer Patient
Version DLQI	Dermatology Life Quality Index
HR-QOL	Health-related Quality of Life
QOL	Quality of Life
RTOG	Radiation Therapy Oncology Group

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CHAPTER 1

INTRODUCTION

Statement of the Problem

Breast cancer is the most prevalent cancer among women worldwide (American Cancer Society [ACS], 2016). See Figure 1.1. Approximately 1.5 million women worldwide were expected to develop breast cancer during 2008 (ACS, 2011).

Additionally, 246,660 women in the U.S. are expected to develop breast cancer in 2016 (ACS, 2016). Most of these women will require radiation therapy.

Although radiotherapy is the standard of care for most breast cancers, it is not without significant iatrogenic sequelae that are likely to have a negative effect on patient quality of life. Up to 100% of women receiving external beam radiation therapy for breast cancer experience grade one or higher radiation dermatitis (Di Franco et al., 2013 [97%]; Diggelmann et al., 2010 [80-90% erythema]; Gosselin, Schneider, Plambeck, & Rowe, 2010 [95%]; Knobf & Sun, 2005 [100%]; López et al., 2002 [91.7% erythema]; Osako et al., 2008 [96% conventional, 83% hypofractionated]). Aside from washing the breast and using IMRT, there is no standard clinical guideline for the prevention and treatment of radiation dermatitis (Pignol et al., 2008; Roy, Fortin, & Larochelle, 2001). Clinical trials of topical agents to prevent radiation dermatitis have demonstrated conflicting results. While there may be reasons related to the agents themselves that lead to inconclusive results, previous studies are flawed in ways that make it difficult to assess

efficacy of the agents. This reflects a number of issues in the design of previous studies: 1) Often only one global assessment of breast skin is conducted weekly, 2) Most studies of radiation dermatitis do not quantitatively or qualitatively measure the patient's symptom experience, 3) There are no skin-related quality of life instruments independently validated for use in radiation dermatitis. As a result, we remain unable to effectively assess the usefulness of topical agents that could decrease suffering, prevent treatment delays or early termination, and improve quality of life for thousands of breast cancer patients. By improving our approach to the assessment of radiation dermatitis and quality of life experienced during this toxicity, we may determine the best methods to prevent and treat this problem. Potential solutions include using a quality of life instrument specifically designed for skin conditions (e.g., the Dermatology Quality of Life Index; Basra, Fenech, Gatt, Salak, & Finlay, 2008) to improve assessment of patient perception of quality of life during the presence of radiation dermatitis and to expand the number of assessments of the breast during radiation therapy from one global assessment to seven sites in the radiation treatment field. This may provide increased sensitivity to small but clinically significant objective changes in radiation dermatitis during intervention studies.

Radiation dermatitis has a profound impact on quality of life. For example, Haas and Moore-Higgs (2010) recount the experience of one patient who commented, "I feel like I am on fire, and I am not sure I want to finish treatment" (p. xiii). Yet little is known about skin-specific quality of life. As suggested by the quote above, patients experiencing severe radiodermatitis may be hesitant to complete treatment. Additionally, skin reactions can lead to radiation treatment delays (i.e., breaks). A delay of more than 1 week may

have a significant adverse impact on treatment outcome (Bese, Sut, & Ober, 2005, 2007). Studies of the prevention and management of radiation dermatitis have varied in method and provided inconsistent results, leading to no clear plan of care (Haas & Moore-Higgs, 2010).

Specific Aims

The primary objectives of this research were to examine the efficacy of and pilot test measures of skin toxicity to be used in a larger future study and gain a better understanding of quality of life among women who are receiving whole breast radiation therapy at a community cancer center for grade 0 to III breast carcinoma.

Specific Aim 1

Determine the feasibility of conducting a future longitudinal study and pilot measures that may better describe radiodermatitis among women with breast cancer.

Sub-aim1.1

To determine the feasibility of recruiting, enrolling, and following women with breast cancer across six time points who are being treated with whole breast radiotherapy.

Sub-aim 1.2

Pilot a collection of measures planned for use in a larger future study.

Sub-aim 1.3

Explore the utility (i.e., usefulness) of clinician-measured breast length (i.e., distance between the inframammary fold and nipple) and participant- reported bra cup size in predicting the development of radiodermatitis over time on treatment and the

efficacy of using multiple measurements of skin toxicity in the treatment field.

Sub-aim 1.4

Calculate effect sizes to allow a scientific estimate of the sample size needed for the future study.

Specific Aim 2

Initiate the validation process of the Dermatology Life Quality Index (DLQI) when used in breast radiodermatitis.

Sub-aim 2.1

Measure the agreement between the participant responses to the DLQI items and their narrative feedback regarding the impact of constructs represented by the DLQI among women with breast radiodermatitis at the 5th week of radiotherapy.

Sub-aim 2.2

Appraise the content validity of the DLQI when used in radiation oncology.

Sub-aim 2.3

Assess the construct validity of the DLQI subscales using principal component analysis.

Sub-aim 2.4

Estimate the reliability of the DLQI subscales when used in our population of women with breast radiodermatitis.

Specific Aim 3

Describe the thoughts and experiences of women experiencing radiation dermatitis of the breast at a cancer program in a community setting as associated with skin-related quality of life.

Specific Aim 4

Investigate the impact of breast radiodermatitis on skin-related and global quality of life among women receiving external radiotherapy.

Sub-aim 4.1

Explore the relationship between skin-related and global quality of life among women experiencing breast radiodermatitis.

Sub-aim 4.2

Describe the change in skin-specific and global quality of life (QOL) among women undergoing external radiation therapy for breast cancer between baseline and at week 5 on radiotherapy.

Organization of the Dissertation

This dissertation is organized into eight chapters. This chapter introduces the statement of the problem, specific aims, and research questions. Chapter 2 provides the background and significance of the breast radiodermatitis, and skin-related and global quality of life. The conceptual model of the study design and methods implemented in the study are explicated in Chapter 3. The next four chapters (i.e., Chapters 4 through 7) are written in journal manuscript format (i.e., American Medical Association style). The

results included in Chapter 4 describe a feasibility and pilot study of breast radiodermatitis. Chapter 4 reflects our findings regarding specific aim 1. The results presented in Chapter 5 describe the initial validation of the Dermatology Life Quality Index (DLQI). This chapter explores specific aim 2. The results in Chapter 6 describe women's perceptions of skin-related quality of life and relate to specific aim 3. The results provided in Chapter 7 describe the impact of radiodermatitis on skin-related and global quality of life. This chapter relates to specific aim 4. The review of pertinent literature and description of methods may overlap between the manuscripts and other chapters in this dissertation. A summary of our study results, limitations experienced, and recommendations for future research and clinical practice is provided in Chapter 8.

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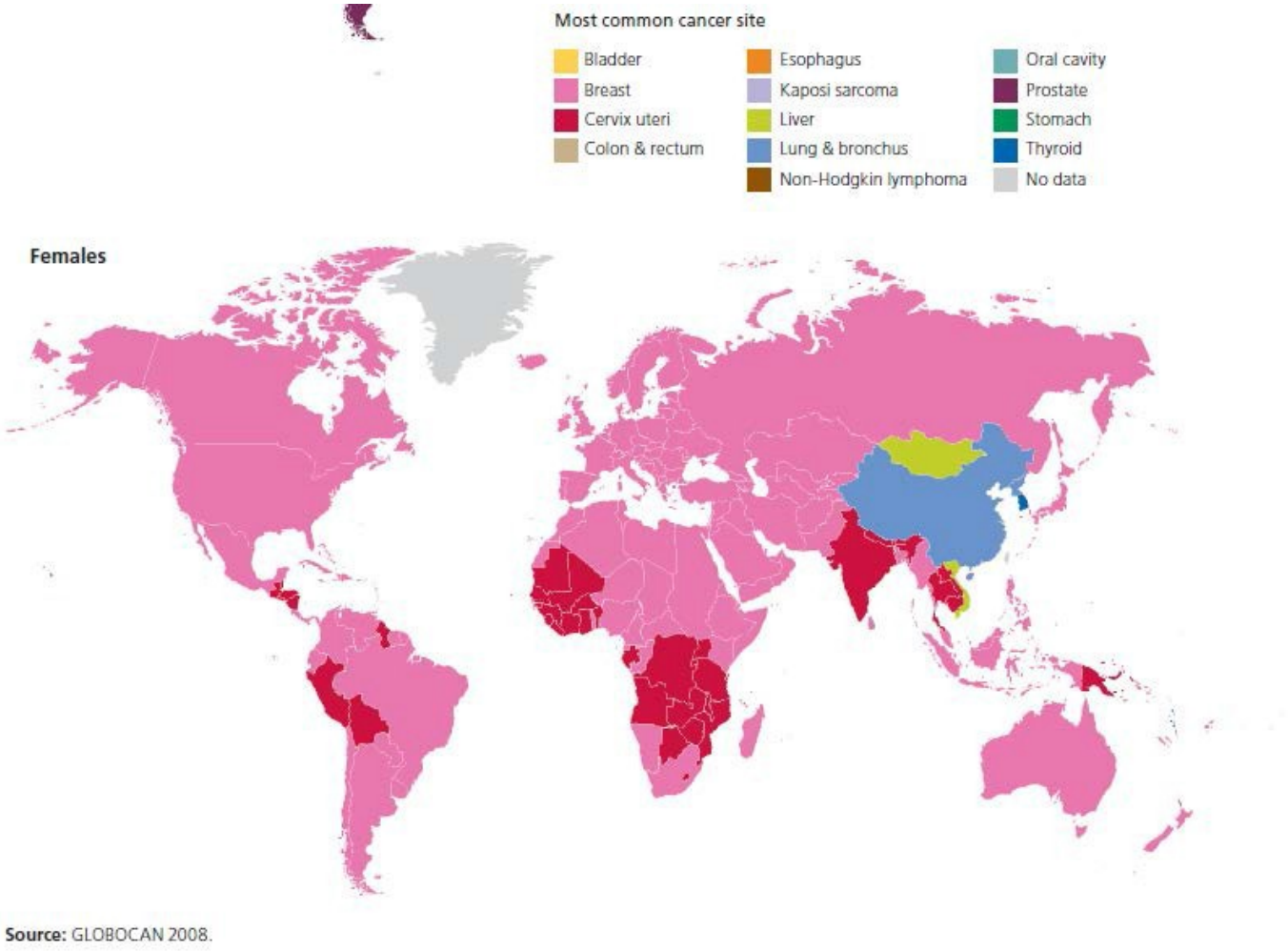

Figure 1.1. Breast cancer is the most frequently occurring cancer among women worldwide. American Cancer Society. *Global Facts and Figures, 3rd edition.* Atlanta, GA; American Cancer Society Inc. Used with permission.

CHAPTER 2

BACKGROUND AND SIGNIFICANCE

Introduction

This purpose of this chapter is three-fold. First, breast cancer and its treatment are described. Second, the pertinent literature regarding radiation dermatitis is reviewed. Third, global and skin-related quality of life are discussed.

Breast Cancer Overview

Breast Cancer Incidence and Mortality

Breast cancer is the most frequently occurring solid tumor and second leading cause of cancer death among U.S. women following lung and bronchus (American Cancer Society [ACS], 2016). During 2016, approximately 246,660 women and 2,600 men will develop breast cancer in the United States and another 40,450 women and 440 men are expected to die of this disease (ACS, 2016). Similar to the U.S., breast cancer is the most common site of primary cancer and the leading cause of cancer death among women across the globe (ACS, 2011). During 2008, 1,383,500 new cases of breast cancer and 458,400 breast cancer-related deaths were expected in women worldwide (ACS, 2011).

Anatomic Pathology in Breast Cancer

Currently, primary breast cancer is defined as a carcinoma (i.e., malignant cells) originating in the breast tissue. Breast cancers are described and classified using a number of methods. Some of these descriptors include depth of invasion, hormone and other receptor status, histologic type, and anatomic stage.

Depth of invasion is an indicator of prognosis. "Carcinoma in situ" refers to a superficial cancer that remains confined to the cells of the tissue of origin; while "invasive" or "infiltrating" refers to a cancer that extends below the basement membrane in the cells of a tissue. Cancers that have not become invasive are more easily cured and less likely to metastasize. Conversely, invasive cancers are more difficult to cure and more likely to metastasize to distant locations.

Healthy breast tissue has hormone receptors for estrogen and progesterone. In nearly two-thirds of breast cancer, the hormone receptors retain their function (College of American Pathologists [CAP] & American Society of Clinical Oncology [ASCO], 2010). The estrogen receptors allow estrogen to stimulate breast cancer growth. The estrogen receptor (i.e., ER) and progesterone receptor (i.e., PR or PgR) status is used to help classify breast cancers (Allred et al., 2009) and portends response to hormonal therapy and survival.

Human epidermal growth factor receptor (i.e., HER) is a constituent of normal breast tissue. In 20-30% of all breast cancers, a specific type of HER called HER2/neu is overexpressed (Yackzan, 2011). Overall, breast tumors that overexpress HER2/neu have a poorer prognosis (Wiseman et al., 2005).

There are several histologic types of breast cancer. The most common types

include invasive ductal, invasive lobular, medullary, tubular, mucinous, inflammatory, and Paget's disease.

Invasive ductal breast carcinoma (IDC) is the most common type and accounts for 65-85% of all breast cancers (College of American Pathologists [CAP], 2011). Breast cancers that cannot be classified as another subtype are known as IDC (Yackzan, 2011). IDCs that are well-differentiated are usually ER and PR positive and HER2/neu negative, while poorly differentiated IDCs tend to be ER and PR negative and HER2/neu positive (Yackzan, 2011).

Tubular breast carcinomas are a subset of IDC. They have a spiculated (i.e., spiked) appearance and are typically found on mammogram among postmenopausal women (Yackzan, 2011). Unlike typical IDC, tubular carcinomas do not frequently spread to the axillary lymph nodes (Yershulami, Hayes, & Gelmon, 2009). They tend to be ER and PR positive, but HER2 negative (Yershulami, Hayes, & Gelmon, 2009).

Invasive lobular breast (ILC) carcinoma is the second most common form and accounts for 10-15% of all breast cancers (CAP & ASCO, 2010). ILCs demonstrate an Indian file pattern where the cancer cells form a single file straight line in the breast stroma (Yackzan, 2011). Like the IDCs, ILCs that are well-differentiated are typically ER and PR positive and HER2/neu negative, while poorly differentiated IDCs are likely to be ER and PR negative and HER2/neu positive (Yackzan, 2011).

Medullary breast cancers (MBCs) tend to occur in younger women with *BRCA1* genetic mutations and grow rapidly (Yackzan, 2011). These cancers tend to appear as benign lesions on medical imaging (Yershulami, Hayes, & Gelmon, 2009). MBCs tend to be ER, PR, and HER2 negative (Yershulami, Hayes, & Gelmon, 2009). The diagnosis of

MBC requires five criteria: 1) a syncytial growth pattern [i.e., multinucleated mass of cytoplasm], 2) a circumscribed border without microinvasion, 3) inflammatory features including large to moderate lymphoplasmacytic infiltrate, 4) a nuclear grade that is poorly differentiated [i.e., appears vastly different from the original tissue], and 5) a high mitotic rate (Rapin et al., 1988; Vincent-Salomen et al., 2007). Although MBCs have these very aggressive pathologic features, they have better outcomes than other breast cancers with similar aggressive pathologic findings, likely due to increased sensitivity to chemotherapy and radiotherapy (Vincent-Salomen et al., 2007).

Mucinous breast cancers have a palpable mass filled with mucin. The mucin creates difficulty in imaging the mass. They tend to be ER, PR, and HER2 positive (Yershulami, Hayes, & Gelmon, 2009). Mucinous breast cancers tend to occur in older women (Yackson, 2011) in their seventh decade (Yershulami, Hayes, & Gelmon, 2009).

Inflammatory breast cancer (IBC) originates on the breast skin and accounts for 1-5% of all breast cancers (Yackson, 2011). IBC causes the breast skin to become erythematous, warm, and tender. These factors can mimic radiation dermatitis. In fact, IBC is often misdiagnosed as a benign dermatitis, is rapidly progressing, and has a survival rate of only 5% (Robertson, 2010). Over half of all IBCs are ER negative and approximately one-third of IBC cases are ER, PR, and HER2 negative (Robertson et al., 2010).

Paget disease is a very rare cancer involving the nipple or areola. Paget's disease causes erythema, irritation similar to eczema, ulceration, and crusting of the nipple or areola (Yackzan, 2011). Most Paget's disease breast cancers are ER and PR negative (Fu, Lobocki, Silberberg, Chelladurai, & Young, 2001).

The "TNM" system is used to stage breast cancer. "T" represents the tumor size in centimeters. "N" represents regional lymph node involvement. "M" represents distant metastases. Stage 0 refers to noninvasive breast cancers. Stage 0 breast cancers include carcinoma in situ and no lymph node or distant site involvement. Stage I includes breast cancers with a tumor size of 20 millimeters or less and no or only microscopic invasion of the lymph nodes. Stage II includes those breast cancers with a tumor size of 50 millimeters or greater or the involvement of up to three axillary lymph nodes. Stage III includes breast cancers with tumors that may extend to the chest wall or involvement of at least four axillary lymph nodes or involvement of the ipsilateral (i.e., same side as breast cancer) internal mammary lymph nodes or involvement of the ipsilateral supraclavicular lymph nodes (American Joint Commission on Cancer [AJCC], 2010).

Stage IV refers to breast cancers that have metastasized to distant locations. In breast cancer, these locations typically include the bones, brain, and lung. Radiation therapy for stage IV breast cancer provides palliative treatment at the distant site.

Treatment of Breast Cancer

The primary treatment for most breast cancers is surgery (National Comprehensive Cancer Network [NCCN], 2015). Surgery typically includes removing the tumor and a small margin of healthy tissue (i.e., lumpectomy, segmentectomy) or removing the breast (i.e., mastectomy) then performing or forgoing reconstruction.

Prognostic factors that estimate the likelihood of cancer recurrence and predictive factors that estimate the likelihood of tumor response to treatment are used to determine whether systemic therapy is indicated (National Cancer Institute [NCI], 2009). Systemic therapies used to treat breast cancer include chemotherapy, hormonal therapy, and

targeted drugs (NCI, 2009). Chemotherapy alone or with radiotherapy added has shown a negative impact on global QOL among breast cancer patients (Marino et al., 2008).

Radiation Therapy

Radiation therapy is a "local" treatment when used for breast cancer. It is administered to specific areas of the breast and sometimes to nearby lymph nodes. According to the American Cancer Society, Surveillance and Health Services Research (2013), a review of the 2008 National Cancer Database revealed that 51% of women with breast cancer in stages I to II and 44% with breast cancer stages III to IV receive some form of radiotherapy. The types of radiation therapy most frequently used to treat breast cancer are described below.

Conventional Radiation Therapy

A linear accelerator is used to provide conventional external beam radiation therapy. The radiation beam travels from the gantry of the linear accelerator to the target on the patient's body. The height and width of the tumor are matched, but healthy tissue is also exposed to radiation. The participants of the current study did not receive conventional radiotherapy.

3-Dimensional Conformal Radiation Therapy

The beams of radiation used in 3-dimensional conformal radiation treatment are shaped to match the tumor. This technique allows better targeting of the tumor with higher radiation doses and sparing of healthy tissue. The participants in the present study received 3-dimensional conformal radiotherapy of the whole breast.

Intensity Modulated Radiation Therapy (IMRT)

IMRT uses hundreds of small radiation beams to conform to the shape of a tumor. Each radiation beam is individually controlled by the treatment plan. The shape of the beam changes hundreds of times during each treatment to focus on the tumor and to spare healthy tissue. IMRT is associated with a decreased, but not completely obviated, incidence and duration of radiation dermatitis (Freedman et. al., 2009; Pignol et al., 2008). IMRT can be provided by some linear accelerators and all tomotherapy units. IMRT was not implemented by the cancer program in the community setting of our study.

Accelerated Radiation Therapy

Accelerated radiation therapy is also administered via a linear accelerator using external beams. The daily dose is increased, but administered in fewer fractions of radiotherapy. Seven participants in the present study received accelerated radiotherapy of the whole breast.

Partial Breast Irradiation

Partial breast irradiation treatment focuses on specific areas of the breast such as the lumpectomy cavity compared to radiation of the whole breast. It is typically administered into the cavity created during lumpectomy, given intraoperatively during breast surgery, or interstitially via thin catheters threaded through breast tissue (Baglan et al., 2003; Williams, 2012). Patients receiving partial breast irradiation were excluded from the current study.

Radiation Boost

A radiation boost is an additional radiation treatment given to a portion of the whole breast treatment field. There are three main types of radiation boosts. They include the operative bed, mastectomy scar, and chest wall boost. Patients with close surgical margins are at greater risk of cancer recurrence in the operative (i.e., tumor) bed, so a larger boost is typically given over seven fractions; while more acceptable margins require a smaller boost given over five fractions (Williams, 2012). The intended purpose of these types of boost is to decrease the risk of local recurrence in those areas.

Breast Radiodermatitis

Pathophysiology

Ionizing radiation creates its effect by knocking or removing electrons from their orbits or shells around the atom, resulting in the atom becoming ionized. Photons are the primary type of ionizing radiation used for whole breast radiotherapy. Photons are a form of electromagnetic radiation consisting of little packets of energy that are generated by a linear accelerator (Ma, 2012). The photons travel through tissue and form ions in the atoms of the cells in the tissue. This change causes damage to the cell's deoxyribonucleic acid (DNA) by breaking the DNA chain leading to cell death or preventing cell replication (ACS, 2014).

There are three stages in the cellular response to ionizing radiation exposure. The first stage is the physical response where ions are formed in the atoms of exposed tissue Ma, 2012). The second stage is the radiochemical response where highly reactive free radicals are formed (Ma, 2012). The third stage is the biologic response where DNA is damaged. Cells exposed to radiation therapy react in one of four ways. First, there may be

no cell injury. Second, the cell may be repaired correctly. Third, a genetic mutation occurs and the cell may be repaired incorrectly. Fourth, the cell dies in response to radiation-induced damaged (Ma, 2012).

Both benign and cancer cells respond differently to radiation exposure. Rapidly dividing cells such as those of the mucosa are particularly radiosensitive, while cells that divide more slowly such as those of the muscles are radioresistant (Ma, 2012).

The trajectory of radiation changes on tissue has been described in the literature. For example, the International Commission on Radiological Protection (ICRP) drafted a report detailing radiation doses, target organs and tissues, radiation changes and the timing of their onset. See Table 2.1. Some tissues respond acutely and while other tissues respond much later to radiation therapy. An acute radiation response is seen within hours to days of exposure. The skin is a tissue that demonstrates an acute response to radiation therapy (Ma, 2012). Acute radiation breast skin changes occur within the epidermis (Jagsi, 2011). Breast "radiation results in deformation of the parenchyma; leading to retraction, fibrosis, vasculitis, and skin breakdown" (Churgin, Isakov, & Yetman, 2008, p. S24).

A late response occurs months to years after radiation therapy. Breast tissue has a late response to radiation therapy (Ma, 2012). The skin may also exhibit a late response to radiation therapy related to damage of the dermis and vasculature (Jagsi, 2011); however, this study does not examine late onset radiation dermatitis.

Acute radiation skin toxicity typically occurs in a predictable order. First, radiation therapy causes an inflammatory response, which leads to dilation of capillaries in the dermis producing a transient erythema in exposed skin. Wells (2004) found that

anemia mitigates radiation-induced skin erythema. Second, DNA damage to the germinal cells of the epidermis, hair follicles, and sebaceous glands leads to loss of the epidermal basal cells, epilation, and dryness of the skin (Lawenda & Johnstone, 2011). Third, erythema becomes more prominent as inflammatory cells migrate into the dermis (Lawenda & Johnstone, 2011). Fourth, the dry skin in the treatment field begins to peel causing dry desquamation. An increased amount of melanin is produced by melanocytes in the basal layer of the epidermis leading to hyperpigmentation (Lawenda & Johnstone, 2011). Fifth, moist desquamation may occur if the cumulative radiation dose to the skin exceeds 40 Gray [Gy] (Lawenda & Johnstone, 2011).

Patient Experience of Radiodermatitis

Radiation dermatitis is a treatment-induced dose-limiting toxicity (Gosselin et al., 2015). The National Cancer Institute (NCI, 2015) defines radiation dermatitis as "a skin condition that is a common side effect of radiation therapy. The affected skin becomes painful, red, itchy, and blistered" (NCI, 2015). Radiodermatitis can lead to treatment delay or early termination, lost work productivity, wound care costs, social isolation, and altered body image (Oncology Nursing Society [ONS], 2015; Schnur et al., 2012). Thus radiodermatitis can greatly impact quality of life (ONS, 2015).

Knobf and Sun (2005) found women undergoing radiotherapy for breast cancer reported experiencing pain, twinges, skin changes, fatigue, sleep disturbances, and breast edema. Comparably, women in a study conducted by Wengström, Häggmark, Strander, and Forsberg (2000) described having pain, skin changes, and fatigue at the end of breast radiotherapy. Moreover, all of the participants in Knobf and Sun's (2005) study experienced a skin change by the 5th week of radiotherapy. Similarly, 100% of the breast

cancer patients in a study by Berthelet et al. (2004) developed skin toxicity during external radiotherapy.

Patient-specific Risk Factors for Breast Radiation Dermatitis

The results of numerous studies conducted over the past two decades have identified predictors of radiation dermatitis development. Decades ago, Porock et al. (1998, 1999) found bra cup ≥ D, body weight, smoking status, skin phototype, lymphocele aspiration, and history of cancer were associated with a severe skin reaction. More recently, De Langhe et al. (2014) found bra cup ≥ D, body mass index (BMI) ≥ 26, current smoking, genetic variation in *MLH1*, concomitant hormone therapy, normofractionation, and IMRT in the supine position modified the risk of developing radiotherapy-induced skin toxicity.

Breast Characteristics

Large breasts are consistently associated with increased risk of radiodermatitis. Studies that have considered breast size have primarily focused on cup size. However, most pairs of breasts are naturally asymmetrical, while bra cups are equal in size making the fit too large or small on one side. In addition, an investigation by Wood, Cameron, and Fitzgerald (2008) in Australia revealed 80% of the study population wore incorrectly fitting bras. Moreover, bra cup size may not identify the amount of breast ptosis (i.e., drooping). Pendulous breasts increase the surface area in the inframammary fold and cause a bolus effect during radiation therapy that predisposes the woman to radiation dermatitis (Algan, Fowble, McNeeley, & Fein, 1998; Barrett-Lennard &Thurstan, 2008). Clinician-measured breast length is a potential solution to these issues that must be tested.

Few studies of radiation dermatitis have included breast measurements such as asymmetry and ptosis as variables. Liu, Luan, Mu, and Ji (2010) used medical imaging to calculate seven unique measurements of the breasts (i.e., nipple level, nipple to midline distance, inferior mammary fold level, breast width, breast projection, breast volume, and anterior chest wall projection) in 100 Chinese women. They found that 100% of the women had at least one of the seven parameters significantly different between the breast pairs. These issues support the need for a more precise measurement of the breast in research studies when breast size is used to predict an outcome such as radiation dermatitis.

Although there are several scales used to measure radiation dermatitis, each instrument usually employs one global assessment of the breast treatment field to identify the maximum level of skin toxicity. However, Hidvegi, Nduka, Myers, and Dziewulski (2004) measured the torso surface area of 40 healthy women to estimate body surface area in burn victims and found that "for every increase in cup size, the surface area of a woman's anterior trunk increased by a factor of 0.1 relative to her posterior trunk area" (p. 1595). These researchers found the pectoral region may account for 10% of the total body surface area when the bra cup size is greater than or equal to DD (Hidvegi, 2004). Therefore, there is a precedent for making multiple assessments of radiation skin toxicity (Hindley et al., 2014; Porock & Kristjanson, 1999; Roper, Kaisig, Auer, Mergen, Molls, 2004). Using a single measurement of skin toxicity in the breast treatment field does not adequately quantify the body surface area impacted by radiodermatitis. The feasibility and efficacy of multiple measurements of radiodermatitis in the treatment field must be explored.

Body Mass Index

Overweight and obesity are related to increased incidence of breast cancer (ACS, 2015). They are also known risk factors for the development of radiation dermatitis (Pommier, Gomez, Sunyach, D'Hombres, Carrie, & Montbarbon, 2004; Twardella et al., 2003). A BMI $\geq$ 25 is overweight and BMI $\geq$30 is obese (Centers for Disease Control and Prevention [CDC], 2015).

Smoking

A strong association exists between smoking during radiation therapy and the development of radiation dermatitis (Kraus-Tiefenbacher et al., 2012; NCI, 2015; Pignol, Vu, Mitera, Bosnic, Verkooijen, & Truong, 2015; Sharp, Johansson, Hatschek, & Bergenmar, 2013). Similarly, Fisher et al. (2000) found a history of lifelong tobacco abstinence was associated with a reduction (p = .026) of radiation dermatitis development. Smoking tobacco causes vasoconstriction of the cutaneous vasculature (Leow, & Maibach, 1998; Monfrecola, Riccio, Savarese, Posteraro, & Procaccini, 1998). This tobacco-induced vasoconstriction was scientifically measured using thermography, laser doppler flowmetry, plethysmography, videomicroscopy, pulse oximetry, and oxygen electrode (Leow, & Maibach, 1998).

Skin Phototype

Fitzpatrick devised a system describing skin types according to risk of developing sunburn (Astner & Anderson, 2004). The system implements six phototypes that range from “do not tan, burn easily” to “become darker, do not burn” (Wolff & Johnson, 2009). Ironically, skin that is darkly pigmented and does not burn but becomes darker is the

phototype that often suffers the most severe radiation dermatitis (Pignol et al., 2008; Yamazaki, 2012). These findings suggest the need for additional studies to explore the use of skin phototype instead of race and ethnicity as a potential predictor of radiation dermatitis development.

Assessment of Radiation Dermatitis

Although there are several instruments used to measure radiation dermatitis, each instrument usually employs one global assessment of the breast treatment field by a radiation oncology health care provider. There is a precedent for making more than one assessment. Porock and Kristjanson (1999) assessed eight sites in the breast treatment field (i.e., sternum, axilla, upper outer quadrant, upper inner quadrant, lower outer quadrant, lower inner quadrant, nipple, inframammary fold). Hindley et al. (2014) measured radiodermatitis in three sites, including near the sternal notch, at three o'clock, and six o'clock on the breast. Röper, Kaisig, Auer, Mergen, and Motis (2004) assessed three sites in the breast treatment field (i.e., upper inner quadrant, upper outer quadrant, inframammary fold). They also measured skin surface dose in these areas, found a higher dose in the inframammary fold, and a lower dose in the other sites. This finding supported the importance of our plan to measure radiation dermatitis in more than one area of the breast. Also, capturing data on the specific location of radiation dermatitis allows for exploration the impact of radiodermatitis by severity and specific site in the radiotherapy treatment field on quality of life.

Nonphysical Sequelae of Radiation Dermatitis

The nonphysical sequelae of radiation dermatitis include treatment delays, early termination of treatment, suffering, and lost contributions to the family and society. Bese, Nut, Sut, and Ober (2007) found a significant difference ($p = .022$) in the 5 and 10 year locoregional control of breast cancer recurrence in favor of women with treatment interruptions of 0-7 as compared to > 8 days. Advanced cancer leads to patient suffering (Cherny, 2009). Illness and premature death of breast cancer patients leads to loss of wages by the patient and family members, loss of contributions to society, caregiving burden on family members, and loss of the patient's role within the family (Yabroff, Lund, Kepka, & Mariotto, 2011).

There are often unrecoverable costs to the patient related to radiation dermatitis (McQuestion, 2006). Schnur, Ouellette, Bovberg, and Montgomery (2012) estimated the mean out of pocket cost of skin toxicity during external beam radiation therapy for breast cancer was $131.64 per patient. Sixty-six percent of the women in the study by Schnur et al. (2012) reported the need to purchase topical products, special soaps, and bandages to manage radiation dermatitis. Additionally, 58% spent money on new bras that provided comfort during therapy, replacement of bras ruined by topical creams or skin markers, or new cotton clothing such as a tee shirt. The costs of purchasing the products and clothing are not covered by health insurance plans and are not eligible expenses for flexible spending accounts (FSAs). In order to utilize money efficiently and reduce human suffering, it is crucial to determine the efficacy of topical agents that may help prevent or manage radiation dermatitis. The measures tested in this study will be utilized in future clinical trials of topical agents.

Global Quality of Life

Most studies on cancer-related quality of life have focused on cancer survivors who have completed treatment, not those actively receiving treatment. However, it is important to study QOL among patients actively receiving treatment because QOL data can be used to predict the onset of cancer treatment-related toxicities (Halyard, Frost, Dueck, & Sloan, 2006). Additionally, QOL data can be used as an endpoint in cancer clinical trials and to guide clinical care as laboratory data do (Halyard et al., 2006).

QOL may decrease or increase in the presence of high toxicity level (Huschka & Burger, 2006). This may occur when bulky cancer is present. Cancer treatment may cause toxicity such as neutropenia while at the same time reducing tumor size and decreasing pressure on nearby structures. This scenario suggests the need for measurement of toxicity and QOL during cancer clinical trials.

Skin-related Quality of Life

Few studies have examined the impact of breast radiodermatitis on QOL as a primary outcome. In a pilot study by Schnur, Ouellette, Bovberg, and Montgomery (2009), breast cancer patients receiving radiotherapy perceived there is a time when symptoms should appear and a time when those symptoms should resolve. These patients feared the symptoms might never end, that they were possibly receiving the wrong treatment, or the cancer may recur. Also, the patients perceived themselves as physically repulsive and felt guilty about not being able to do everything they did before the breast cancer diagnosis. In a second larger study, breast cancer patients commented that sunburns go away, but radiation burns keep getting worse. They were anxious for their skin's appearance to return to normal (Schnur, Ouellette, Dilorenzo, Green, &

Montgomery, 2011). Lighter skinned women talked about their skin getting red, for example, "you couldn't even find the nipple on my breast" (Schnur et al., 2011, p. 263). Darker skinned women commented about their skin getting darker, for example, "dark and ugly, too dark, like toast when it burns, black and crispy, burnt, and charcoal" (Schnur et al., 2011, p. 263). The women voiced concerns about discomfort, treatment interruptions because of radiation dermatitis, and lengthened treatment plans caused by the treatment interruptions (Schnur et al., 2011). They often needed to adapt their clothing and this impacted their social activities. The women commented about having to go braless, changing from an underwire bra to one without an underwire, wearing a camisole or undershirt; or needing to wear loose clothing, only black bras, or old t-shirts because of greasy, oily skin creams (Schnur et al., 2011). Large breasted women discussed inability to go to church and family functions such as weddings because they were unable to wear an underwire bra (Schnur et al., 2011). This finding was also supported by the study of a topical agent to prevent radiation dermatitis in breast cancer patients. Of the 42 patients who completed the study, 44% reported having trouble wearing a brassiere by the end of radiation treatment (Szumacher et al., 2001). These results of these studies demonstrate the detrimental impact of radiodermatitis on skin-related QOL. Further, skin-related QOL needs to be measured as a primary outcome in studies of radiodermatitis.

Significance of Study

Radiation dermatitis is a significant concern for women receiving radiotherapy for breast cancer and their health care providers. The only evidence-based guideline for breast skin care during radiotherapy is to wash the radiation treatment field daily to

prevent infection (Roy, Fortin, & Larochelle, 2001). There are no clear guidelines for the prevention and management of radiation dermatitis of the breast. Expanding the assessment of breast skin toxicity to include seven areas within the treatment field may increase our ability to detect small but clinically significant changes during future clinical trials of agents that may prevent or manage radiation dermatitis. In addition, the patient's perspective is an important component of the radiation dermatitis experience. Measuring the patient's quality of life during breast radiation therapy helps elucidate the patient's perspective.

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Table 2.1

Effect of Radiation Therapy on Normal Tissues and Organs

Effect	Approximate threshold doses (Gy)	Time of Onset
Early transient erythema	2	2-24 hours
Main erythema reaction	6	~1.5 weeks
Temporary epilation	3	~3 weeks
Permanent epilation	7	~3 weeks
Dry desquamation	14	~4-6 weeks
Moist desquamation	18	~4 weeks
Secondary ulceration	24	>6 weeks
Late erythema	15	8-10 weeks
Ischaemic dermal necrosis	18	>10 weeks
Dermal atrophy (1st Phase)	10	>52 weeks
Telangiectasia	10	>52 weeks
Dermal atrophy (Late Phase)	>152	>52 weeks

International Commission on Radiological Protection. (2011). Draft: Early and late effects of radiation in normal tissues and organs: *Threshold doses for tissue reactions and non-cancer effects of radiation protection context*. p. 76. Used with permission.

CHAPTER 3

RESEARCH DESIGN AND METHODS

Research Design

We conducted a longitudinal, mixed methods, pilot and feasibility study. Measures to be used in a larger study were piloted and we examined the feasibility of our measures. Measurements of skin toxicity and skin-related quality of life (QOL) were taken at baseline and repeated during weekly radiation therapy. Global QOL was measured at baseline and repeated at the 5th week of radiotherapy. Change was measured within each participant. The validation process for use of the Dermatology Life Quality Index (DLQI) in breast radiodermatitis was initiated. A content analysis was conducted on participant's narrative comments regarding the most important item on the DLQI.

Conceptual Model

We hypothesized that whole breast external radiotherapy, physical characteristics such as skin phototype and breast size, and lifestyle behaviors including smoking and body mass index (BMI) would influence the physical changes that are collectively described as radiodermatitis. We further hypothesized that radiodermatitis would impact skin-related and global QOL. A conceptual model that illustrates our study design is presented in Figure 3.1. This conceptual model is based on the researchers' empirical

knowledge and the components are supported by studies reported in the professional literature. For example, conventional external beam radiotherapy of the whole breast (Pignol et al., 2008), physical characteristics including skin phototype (Yamazaki et al., 2011) and breast size (Algan, Fowble, McNeeley, & Fein, 1998; Barrett-Lennard, Thurstan, 2008; De Langhe et al., 2014; Pommier, Gomez, Sunyach, D'Hombres, Carrie, & Montbarbon, 2004), and lifestyle- related factors such as obesity (De Langhe et al., 2014) and being a current smoker (De Langhe et al., 2014; Sharp, Johansson, Hatschek, & Bergenmar, 2013; Wells et al., 2004) are postulated risk factors for radiodermatitis development. Radiodermatitis impacts skin-related QOL. It often results in physical discomfort (Gosselin et al., 2015; Knobf &, Sun, 2005; Schnur, Ouellette, Bovberg, & Montgomery, 2009; Schnur, Ouellette, Dilorenzo, Green, & Montgomery, 2011; Wengström, Häggmark, Strander, and Forsberg, 2000), bother from radiodermatitis treatment (Schnur et al., 2011), and impacts clothing selection (Schnur et al., 2011, Schnur et al., 2012). Global QOL may also be impacted by radiodermatitis. Domains of global QOL negatively affected by radiodermatitis include physical well-being (Schnur et al., 2011; Sutra, Tan, Freedman, Troxel, & Lin, 2013; Welzel et al., 2013), psychological well-being (Schnur et al., 2011), social well-being (Schnur et al., 2011), and spiritual well-being (Schnur et al., 2011). Additionally, radiodermatitis and poor QOL can lead to delays or early termination of radiotherapy, which impacts treatment efficacy (Bese, Nut, Sut, & Ober, 2007; Gosselin et al., 2015).

Setting and Sample

Setting

This study was conducted at a single site in the department of radiation oncology at an American College of Surgeons Commission on Cancer accredited Comprehensive Community Cancer Program located in northern Illinois. The cancer program had 216 analytic cases of breast cancer during calendar year 2014 (Sebastian & Moerschbaecher, 2015).

Ethical Approval

Ethical approval was gained from the University of Utah Institution Review Board (UIRB), Salt Lake City, Utah, USA. A reliance agreement was created between the UIRB and the health care system affiliated with the cancer program. All participants gave informed consent before inclusion in the study. The data were stored digitally on a secure, password-protected, encrypted, external hard drive. The paper consent forms and external hard drive were secured in a fireproof safe in a locked office when not in use.

Sample

It is appropriate to recruit a purposive sample for a pilot descriptive study of women with breast radiodermatitis (Trochim & Donnelly, 2008). Therefore, a purposive sample of 41 English-speaking adult women with stage 0-III breast cancer identified as candidates for external beam radiotherapy were accrued to the study from May 2014 through May 2015. One participant withdrew from the study during the 1st week. All of the remaining 40 participants were followed from baseline to completion of radiotherapy and completed all study measures.

Inclusion and Exclusion Criteria

A full listing of the study inclusion and exclusion criteria is provided in the study schema illustrated in Figure 3.2. Study participation was restricted to female participants 18 years or older since breast cancer is rare in men and children. Less than 1% of breast cancers occur in men (Giordano, Cohen, Buzdar, Perkins, & Hortobagyi, 2004) and men with breast cancer rarely require radiotherapy to manage their disease (Borgen et al., 1992). Similarly, less than 0.1% of all breast cancer cases occur in children or adolescents (Gutierrez, Housri, Koniaris, Fischer, & Sola, 2008).

Cases of inflammatory breast cancer and Paget's disease of the nipple were excluded from the study because those conditions may appear very similar to radiation changes in breast skin. Additionally, participants with an inflammatory skin condition present on the breast were excluded from the study.

Stage IV breast cancer typically represents metastasis to the brain, bones, or lungs and is treated with radiation therapy to the metastatic site(s). For that reason, cases of stage IV breast were excluded from this study. Any stage of breast cancer requiring external radiation therapy to the breast was eligible for this study. Moreover, the participant must have been scheduled to receive, but had not yet started, external beam breast radiation therapy; those receiving partial or no breast irradiation were excluded.

The principal investigator speaks only English and the radiation skin changes form was available exclusively in English. Consequently, study participation was restricted to women who spoke and read in English.

Sample Size and Sensitivity Analysis

Recommended sample size for pilot studies is a contentious topic and suggestions have ranged from 12 subjects per arm to totals of 30 to 50 subjects (Julious, 2005; Lancaster, 2004; Sim & Lewis. 2004). We sought to have sufficient power to accurately detect significant differences in our larger pilot study looking at the impact of radiodermatitis on skin-related quality of life. However, we did not have a good estimate of this effect. A sensitivity analysis was conducted using G*Power version 3.1.9.1, with a sample size of 40 participants in one group, .10 alpha level of significance, power of .80, epsilon of 1.0, correlation of .50, and six repeated measurements. Using these parameters, we could expect to detect an effect size of .15, which is a small effect size using Cohen's criteria (Cohen, 1992). Since we planned to conduct a descriptive feasibility and pilot study, a slightly relaxed level of significance was acceptable in that it help us avoid missing small but clinically significant differences. Similarly, Rubenstein et al. (2005) argued that a relaxed level of significance is appropriate to a phase II study in that it would be adequate evidence to motivate further investigation of the therapy.

Radiation Treatment

The external treatments were delivered via a Varian Clinac EX linear accelerator using 3-dimensional conformal techniques, including stand open field, hard and enhanced dynamic wedges, and irregular surface compensation. All of the patients were treated in the supine position using photons. Thirty-three women received normofractionated (i.e., 180-200 cGy) doses and 7 women received accelerated treatment using fractions of 266 cGy. The radiation treatment plan (i.e., normofractionated, accelerated) was recorded

at the start of the study. The cumulative radiation dose, energy, fraction number, use of a breast immobilizer or bolus pad was recorded weekly.

Instruments, Forms, and Measures

This section focuses on the study instruments, forms, and measures. A tabular overview of the study tools to be used in the proposed study can be found in Table 3.1. All of the data were collected using hard copies of the instruments and forms.

A packet of baseline surveys and forms in addition to the weekly Dermatology Life Quality Index (DLQI) forms were given to the participant after consent was obtained. The participant was allowed to complete the forms at home or at the cancer center and return the baseline forms to the PI on the first day of radiotherapy. Further, the participant was asked to return a completed DLQI "form" each week on the day of skin assessment.

Measurement of Radiation Dermatitis

Radiation Therapy Oncology Group (RTOG) Acute Morbidity Scoring Criteria--Skin

The acute version of the morbidity scoring criteria for radiation skin reactions was developed in 1985 by the RTOG to complement the existing version for scoring chronic skin reactions and is a standard of care in the radiation oncology community (Cox, Stetz, & Pajak, 1995; Pires, Segreto, & Segreto, 2008). These scoring criteria include five ranked responses from zero—no change over baseline to four—ulceration, hemorrhage, and necrosis. The Radiation Therapy Oncology Group (RTOG, 2015) Acute Morbidity Scoring Criteria—Skin was used to standardize measurement of skin

toxicity in our study. See Figure 3.3. The PI was the sole rater of skin toxicity. Skin toxicity was measured at baseline to establish the normal appearance of skin in the radiation treatment field before radiotherapy commencement, typically at the simulation visit.

Maximum Skin Toxicity

The maximum grade of skin toxicity in the radiation treatment field was assessed at baseline and weekly during radiotherapy by the PI using the RTOG Acute Radiation Morbidity Scoring Criteria for skin (RTOG, 2015). This single measurement of maximum skin toxicity (i.e., RTOG score) is used in clinical settings and research studies.

Breast Skin Assessment Form (BSAF)

Using a single measurement of the maximum radiodermatitis grade has limitations. It does not take into account the amount of body surface area and the location of radiodermatitis. The BSAF is an investigator-developed data collection form. It allows documentation of the RTOG skin toxicity score among seven areas in the breast radiation field (i.e., upper and lower outer quadrant, upper and lower inner quadrant, inframammary fold, sublavicular area, and axilla). These seven areas were assessed at baseline and weekly during radiotherapy exclusively by the PI.

Skin Phototype

Fitzpatrick devised a system describing skin types according to risk of developing sunburn (Astner & Anderson, 2004). The potential ratings included the following: type I—always burns, never tans, type II—always burns easily, tans minimally, type III—

burns moderately, tans uniformly, type IV—burns minimally, always tans well, type V—rarely burns, tans profusely, and type VI—never burns (Wolff & Johnson, 2009). For this study, the skin phototype was determined by the PI once during a short interview with the participant.

Biometrics

Height and weight were measured at baseline; then the BMI was calculated using the online Centers for Disease Control and Prevention (2015) Adult BMI Calculator. Participant-reported bra cup and band size was recorded. The PI measured the length of the affected breast in women who underwent lumpectomy or mastectomy with immediate reconstruction. The contralateral breast was measured in women who underwent mastectomy without reconstruction. The measurement was standardized by using the midclavicular line as a landmark, then measuring the breast length from inframammary fold to nipple in centimeters using a 72" disposable paper measuring tape. The PI measured the breast length for each participant. A case of 500 Medline measuring tapes was ordered to ensure the use of a standardized measurement tool throughout the study while reducing the risk of communicable diseases.

Measurement of Quality of Life

Dermatology Life Quality Index (DLQI)

The purpose of the DLQI is to provide a simple and reliable instrument that can be easily and routinely administered in a clinic setting for any skin condition. It was translated into 55 languages and used for at least 33 skin conditions (Basra, Fenech, Gatt, Salek, & Finlay, 2008). The DLQI was initially developed from information provided by

120 dermatology patients who answered an open-ended question about how their skin condition impacted their life (Finlay & Khan, 1994). Next, 49 aspects of impact on life were identified in the first 70 responses (Finlay & Khan, 1994). No new aspects emerged in the remaining 50 responses (Finlay & Khan, 1994). The aspects were ranked by frequency of citation and 10 aspect-based questions were developed (Finlay & Khan, 1994). The 10-item instrument was piloted in 20 patients, revised slightly, and then piloted again in another 20 patients (Finlay & Khan, 1994). The DLQI contains 10 scaled items including one that is partly dichotomous. The scaled items focus on physical sensations; embarrassment; interference with activities at home; clothing selection; impact on social activities; difficulty participating in a sport; causing a problem at work or school; causing a problem with relationships among close friends, relatives, or a partner; sexual difficulties; and impact of treatment on life and lifestyle. The dichotomous item inquires whether or not the skin condition prevented the respondent from attending work or school. The 10 DLQI items can be grouped into six subscales for analysis including: 1) symptoms, feelings [items 1 & 2], 2) daily activities [items 3 & 4], leisure [items 5 & 6], work/school [item 7], personal relationships [items 8 & 9], and treatment [item 10] (Finlay & Khan, 1994). Eight of the scaled items include options of "very much," "a lot," "a little," "not at all," and "not relevant." Two additional items include the previous options except "not relevant." A DLQI cumulative score of 0-1 represents no effect, 2-5 represents a small effect, 6-10 represents a moderate effect, 11- 20 represents a very large effect, and 21-30 represents an extremely large effect on the patient's life (Department of Dermatology, 2011).

Internal consistency is the form of reliability that measures the degree to which

items in a scale measure the same construct and is expressed in the form of Cronbach's alpha with scores ranging from .0 to 1.0. A high Cronbach's alpha suggests the instrument is consistent and reliable. A score of at least .70 is desirable (DeVellis, 2003) and .80 is preferable (Pallant, 2010). Conversely, a score of 1.0 suggests the presence of redundant items. A study of the DLQI in patients with eczema, an inflammatory skin condition similar to radiation dermatitis, revealed a Cronbach's alpha of 0.83 (Badia, Mascaro, & Lozano, 1999), a good-to-excellent score. A review of 22 studies using the DLQI for psoriasis, acne, burn scars, urticaria, melasma, and other dermatologic conditions yielded a Cronbach's alpha range of 0.75 to 0.92 (Basra et al., 2008).

Validity is the extent to which an instrument measures what it is intended to measure. The degree to which an instrument adequately samples the phenomenon of interest is known as content validity. The DLQI was originally developed from the input of 120 dermatology patient's responses to the request, "Please could you write down all the ways that your skin disease affects you" (Finlay & Khan, 1994, p. 210). This process ensured the content of the DLQI contained items that dermatology patients deemed important to their QOL. Next, the DLQI was pilot tested in 20 patients and minor changes were made (Finlay & Khan, 1994). Finally, the DLQI was tested in another 20 patients to verify content validity (Finlay & Khan, 1994).

Face validity focuses on whether an instrument measures what it proposes to measure (Doordan, 1998). Face validity is a subjective measure, while content validity is an objective measure of the instrument's adequacy in measuring the phenomenon of interest.

No studies were found that addressed the face validity of the DLQI. Therefore, we

solicited feedback on the DLQI from expert 12 radiation oncology nurses at a local chapter meeting of the Oncology Nursing Society. A hard copy of the DLQI was given to each nurse. Each nurse was instructed to read the items on the DLQI and provide written feedback on the items.

Quality of Life Instrument—Breast Cancer Patient Version

This instrument measures global QOL in patients with breast cancer. The scale consists of 46 items with ordinal ranked responses. The 46 items measure four domains of QOL including physical, psychological, and spiritual well-being, plus social concerns. The QOL Instrument—Breast Cancer Patient Version is based on the QOL Instrument—Cancer Survivor (QOL-CS). One question focusing on concern about female relatives' risk of developing breast cancer was added to the original version. The original QOL-CS was developed from items on a survey mailed to 686 cancer survivors, including 294 survivors of breast cancer (Ferrell & Grant, 2003). Test-retest reliability was measured by selecting a random sample of 150 from the original 686 participants. The test-retest reliability for the entire QOL-CS tool was $r = 0.89$ and for the subscales was $r = 0.88$ for physical well-being, $r = 0.88$ for psychological well-being, $r = 0.90$ for spiritual well-being, and $r = 0.81$ for social concerns. Internal consistency was measured using Cronbach's alpha coefficient to quantify the level of agreement between the items and subscales. Ferrell, Hassey Dow, and Grant, (1995) found $r = 0.93$ for the entire scale and alphas of $r = 0.71$ for the spiritual, $r = 0.77$ for the physical, and $r = 0.89$ for the psychological well-being; $r = 0.81$ for the social concerns subscales (Ferrell et al., 1995). A panel of QOL researchers and oncology nurses assessed the content validity of the QOL-CS. A stepwise multiple regression revealed that 17 variables accounted for 91% of

the variance in global QOL (Ferrell et al., 1995). Pearson correlations were used to measure parallel validity between the QOL-CS scale and subscales and the already established Functional Assessment of Cancer Therapy-General (FACT-G) scale and subscales. The correlation between the two overall scales was $r = .78$, the physical subscales was $r = .74$, the social subscales was $r = .44$, and QOL-CS psychological to FACT-G emotional was $r = .65$ (Ferrell et al., 1995). The FACT-G does not have a spirituality subscale. Global QOL was measured in our study using the Quality of Life Instrument—Breast Cancer Patient Version at baseline and at 5 weeks on treatment when the peak severity of radiation dermatitis was expected to begin.

Radiation Skin Changes Questions Form

These questions were designed for this study to delineate differences in constructs on the first item of the DLQI (i.e., itching, pain, stinging) in relation to radiation dermatitis and to explore convergence or divergence between the participant's responses on the DLQI items and her narrative response to how each item on the DLQI impacted her life. The participant was asked to describe the impact of the given DLQI item on her life in writing on the form. The participants completed this form during the 5th week of radiotherapy.

Measures Implemented to Minimize Missing Data

Missing data compromises the validity of study data and findings. External beam radiation therapy is typically delivered daily Monday through Friday. The principal investigator endeavored to collect the weekly measurements on Mondays. This strategy provided four additional daily opportunities (i.e., Tuesday, Wednesday, Thursday,

Friday) to collect data missed on Monday.

Measures Implemented to Maximize Data Security

Each participant was assigned a unique identifier. The unique identifier was used on all study forms and in the database instead of personal identifiers. Hard copies of primary data sources were stored in locked water-proof and fire-proof safe in the principle investigator's (PI) locked office. There was only one clinical site for this study. The log that linked the participant to the data was saved to the cancer program's tumor registrar's password protected secured server. The primary data sources (i.e., study forms) with unique identifiers were transported via a locked suitcase from the radiation oncology department to the PI's automobile and locked in the trunk before transport to the study computer. De-identified data from the study forms were manually entered into the database by the PI on a password-protected, encrypted computer and stored on a secured server. The principal investigator (PI) was the only individual with access to the password and encrypted database.

Data Management and Analysis

Statistical Software

The IBM Corporation (2012) Statistical Package for the Social Sciences (SPSS) Statistics for Windows Version 21.0 was used to create a database and analyze the quantitative data collected.

Clinical Significance Determination

The determination of a *statistically* significant difference or change is made using mathematical calculations and depends on the size of the difference or change (Hinkle,

Wiersma, & Jurs, 2003). However, the determination of a *clinically* significant difference or change is dependent upon the unique patient, the patient's disease status, the patient's perception about QOL within the context of her or his situation, and the viewpoint of the healthcare provider (Symonds, Berzon, Marquis, & Rummans, 2002). Osoba (2011) commented that currently there is no "clear method for determining the clinical meaningfulness of changes in scores" (p. 57). However Frost, Bonomi, Ferrans, Wong, and Hays (2002) remarked that a clinically significant change is one perceived as beneficial or detrimental, important, or a reason to seek healthcare or a change in healthcare. In addition to the need to identify a clinically significant change in one score, there is the challenge of determining the meaning of change over multiple points in time (Cella, Bullinger, Scott, & Barofsky, 2002) and identifying change in qualitative information without interjecting researcher bias. Triangulation is used to establish convergent validity between qualitative and quantitative data (Hussein, 2009). Triangulation "simply means that a particular phenomenon is assessed in multiple modalities" (Knauper & Klein, p. 125). We used participant ratings on the DLQI and their narrative feedback on the radiation skin changes form to triangulate our results and estimate the convergent validity of the DLQI.

Analysis of Research Questions

Specific Aim 1

Describe the development of radiation dermatitis among women with breast carcinoma.

Sub-aim1.1

To determine the feasibility of recruiting, enrolling, and following women with breast cancer who are being treated with whole breast radiotherapy across six time points: The framework created by Thabane et al. (2011) informed the assessment of the feasibility of our pilot study measures (i.e., sub-aims 1.1 & 1.2). See Table 3.2.

Sub-aim 1.2

Pilot a collection of measures planned for use in a larger future study: A number of measures typically used in studies of breast radiodermatitis were piloted. We also conducted a pilot test of two new measures, clinician-measured breast length and ratings of skin toxicity using the RTOG grade in seven areas of the treatment field. Additionally, we explored participant tolerance of completing the DLQI weekly and the COH-QOL-breast at baseline and 5 weeks on radiotherapy.

Sub-aim 1.3

Explore the utility (i.e., usefulness) of clinician-measured breast length (i.e., distance between the inframammary fold and nipple) and participant-reported bra cup size in the development of radiodermatitis over time on treatment and the efficacy of using multiple measurements of skin toxicity in the treatment field. Each participant's breast length was measured by the PI. The resulting value was used as a variable in the correlation and as a comparator to participant-reported bra size in a table. A one-way within-subjects repeated measures ANOVA was conducted to compare skin toxicity grade of the breast using the RTOG scoring system by each individual area in the radiation treatment field and the total of all scores at baseline then weeks 1, 2, 3, 4, and 5

on external radiation therapy.

Sub-aim 1.4

Calculate effect sizes to allow a scientific estimate of the sample size needed for the future study: The effect size for RTOG score by site in the radiation field was calculated during the one-way within-subjects repeated measures ANOVA. Kendall's tau is a nonparametric correlation used instead of a Spearman Rho correlation when the sample size is small and there are tied ranked scores (Field, 2009a). Therefore, a Kendall's tau correlation was performed to measure the relationship between factors and the severity of radiation dermatitis at 5 weeks on external radiotherapy of the breast since our sample was small. However, effect sizes can be calculated by squaring the value of *r* from the Kendall's tau correlation (Walker, 2003)

Specific Aim 2

Investigate the impact of breast radiodermatitis on skin-related and global quality of life among women receiving external radiotherapy.

Sub-aim 2.1

Explore the relationship between skin-related and global quality of life among women experiencing breast radiodermatitis: A Kendall's tau correlation was conducted to describe the relationship between skin-related and global QOL at week 5 on radiotherapy.

Sub-aim 2.2

Describe the change in skin-specific and global quality of life (QOL) among women undergoing external radiation therapy for breast cancer between baseline and at week 5 on radiotherapy: Paired *t*-tests were used to measure the change in skin-related and global QOL from baseline to the 5th week on radiotherapy.

Specific Aim 3

Initiate the validation process of the Dermatology Life Quality Index (DLQI) when used in breast radiodermatitis.

Sub-aim 3.1

Measure the participant agreement between the responses to the DLQI items and narrative feedback regarding the impact of constructs represented by the DLQI among women with breast radiodermatitis at the 5th week of radiotherapy: We measured the concurrent validity of the DLQI by assessing the agreement between participant's responses on the DLQI and their narrative responses to a survey about the DLQI, both at 5 weeks on radiotherapy. Participant agreement was measured at 5 weeks on treatment when skin toxicity begins to peak. An extra copy of the DLQI and the only copy of the radiation skin changes form were given to the participant. Each woman was instructed to look at the extra copy of DLQI. Next, participants were invited to write narratives about how each item on the DLQI impact their life. Thirty-one (78%) of the 40 participants provided narratives. The principal investigator (PI) abstracted the week 5 responses and the narratives on impact and entered the data into a form with a column for the ordinal score on the DLQI (i.e., very much, a lot, a little, not at all), a column for a verbatim

copy of the narrative, and a column for researcher rated level of agreement. Three researchers jointly coded the agreement score for each DLQI participant rating and narrative for the first participant. Subsequently, each researcher coded her perceived level of agreement for the remaining participant responses independently. The PI combined the agreement ratings by each researcher into one master document. The document was shared with each researcher, the agreement ratings were discussed, and consensus formed for items on which the agreement ratings did not originally agree.

Sub-aim 3.2

Appraise the content validity of the DLQI when used in radiation oncology. In this study, it was assessed by soliciting feedback on the DLQI from expert 12 radiation oncology nurses at a chapter meeting of the Oncology Nursing Society. A hard copy of the DLQI was given to each nurse. The nurse was instructed to read the items on the DLQI and provide written feedback on the items. The radiation oncology nurses did not recommend the addition or deletion of any DLQI items. They suggested a few minor word changes. For example, "not relevant" might be changed to "does not apply." We determined the content validity of the DLQI was sufficient for use in our study based on the radiation oncology nurse expert opinions.

Sub-aim 3.3

Assess the construct validity of the DLQI using principal component analysis: Construct validity focuses on the extent that items on a measure such as the DLQI are consistent with the concept of interest (Soeken, 2010). It was assessed using principal component analysis (PCA) of the DLQI subscales. A variety of participant per factor

ratios are suggested in the professional literature, ranging from 3 to 15 participants for each factor (Catell, 1978; Gorsuch, 1983; Pearson & Mundform, 2010; Pett, Lackey, & Sullivan, 2003; Nunally, 1978). We had 40 participants and five subscales yielding a ratio of 8:1. Our sample size adequacy was also estimated post hoc by examining the Kaiser-Meyer-Olkin (KMO) statistic and communalities after extraction, both with values greater than 0.5 if the sample size is adequate (Field, 2009). The SPSS computer application removed the work and study subscale from the PCA because the variance in participant responses was zero for this subscale.

Sub-aim 3.4

Estimate the reliability of the DLQI when used in our population of women with breast radiodermatitis: The reliability of the DLQI subscales was assessed using a Cronbach's alpha analysis and examining the interitem correlations. An alpha of 0.7 or higher and interitem correlation of 0.3 or greater was considered acceptable (Fields, 2009b).

Specific Aim 4

Describe the thoughts and experiences of women experiencing radiation dermatitis of the breast at a cancer program in a community setting as associated with skin-related quality of life: Using directed content analysis, we measured the content validity of the DLQI for use in women with breast radiation dermatitis.

Participants in the main study were asked to complete an open-ended survey about items on the Dermatology Life Quality Index instrument (Department of Dermatology, Cardiff University, 2014). The last question on the survey inquired,

"Which issue is most important and why?" The survey was provided in hard copy at the 5th week on radiation therapy when radiodermatitis was likely to start peaking. The participant was asked to complete the survey and return it within one week. The handwritten responses were transcribed verbatim into a single digital text file by the first author.

Our goal was to gain a greater understanding of patient-reported skin-related quality of life in the presence of breast radiodermatitis. A qualitative content analysis approach was implemented. This research method uses a flexible yet systematic classification process of coding and identifying themes to permit the subjective interpretation of the content of data (Hsieh, & Shannon, 2005). However, reliability is also important (Schreier, 2012).

Each member of the investigative team independently reviewed all of the comments. A list of initial codes was generated during telephone conferences and via email conversations. The first and second author independently assigned codes to the data. The responses were divided to represent one unique concept. None of these concepts were assigned more than one code. The third author reviewed the coded data and provided input. The results were discussed and consensus was reached. The first author reviewed the coded data to identify final codes and overarching themes. Since the participant was completing a survey about the 10 items on the DLQI, the six conceptual domains of this instrument (i.e., symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment) influenced participant's responses and informed some of the themes identified.

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Table 3.1

Study measures, forms, and instruments

Measure, Form, or Instrument	**Description**	**Completed By**	**Frequency of Administration**
Breast Skin Assessment Form (BSAF)	The BSAF is a data collection form. It features a diagram of the breast and seven specific sites in the typical breast radiation field (i.e., upper medial quadrant, upper lateral quadrant, lower medial quadrant, lower lateral quadrant, inframammary fold, axilla, and subclavicular area) that are evaluated using the RTOG Acute Morbidity Scoring Criteria—Skin. It also has an area to record the current cumulative radiation dose and which breast is receiving treatment.	Researcher	Repeated; baseline and weekly
Cumulative Radiation Dose	The cumulative radiation dose was be recorded on the *Breast Skin Assessment Form* at each measurement period. This information will be obtained from the treating Radiation Therapist or from the patient's health record.	Researcher	Repeated; baseline and weekly
Dermatology Life Quality Index (DLQI)	The DLQI is a 10-item questionnaire completed by the participant. It measures skin-specific QOL.	Participant	Repeated; baseline and weekly
Fitzpatrick Skin Phototype	The skin phototype was calculated by recording the participant's eye and natural hair color, and history of freckling, sun-burning, or sun-tanning.	Researcher	Single, measured at baseline
Breast Length	Using the midclavicular line as a landmark, the breast length from inframammary fold to nipple in centimeters using a 72" disposable paper measuring tape.	Researcher	Single, measured at baseline
Quality of Life Instrument--Breast Cancer Patient Version	This is a 46-item scale that measures QOL among breast cancer patients. The 46-items are divided among four domains (i.e., psychological, physical, and spiritual well-being, and social concerns.	Participant	Repeated; baseline, week 5,
Radiation Skin Changes Questions	These questions are designed to delineate differences in constructs on the first item of the DLQI and to explore convergence or divergence between the participant's responses on the DLQI and their narrative responses to the questions.	Participant	Single, measured at week 5
RTOG Acute Morbidity Scoring Criteria-Skin	This single-item, 5-point scale was developed by the Radiation Therapy Oncology Group to objectively assess skin toxicity during therapeutic radiation treatment.	Researcher	Repeated; baseline and weekly

Table 3.2.

Rationale for Conducting a Pilot and Feasibility Study

Main Reason	Explanation
Process	To assess the feasibility of the processes key to the success of larger, funded future studies --Recruitment of women with breast cancer receiving radiotherapy --Retention rates of women with breast cancer receiving radiotherapy --Refusal rates --Appraisal of eligibility criteria --Determine the best process for larger studies
Resources	Assess time and resource problems that might occur in larger, funded future studies --Determine the actual length of time required to complete study measures --Participant --Research team --Determine the human resources required for larger studies --Type of research team members needed --Number of each type of research team members needed
Management	Identify human and data management problems before commencing a larger study --Appraisal of study measures --Additions needed? --Deletions needed? --Identify problematic items before commencing a larger study --Are there any problems entering data into database?
Scientific	Identify the effect of external breast radiotherapy on women --Calculate change in skin toxicity score from baseline to 5 weeks after baseline Identify the effect of radiation dermatitis on QOL in women --Calculate change in QOL score from baseline to 5 weeks after baseline Use this information to conduct power analysis to estimate sample size requirements for grant applications to fund larger future studies.

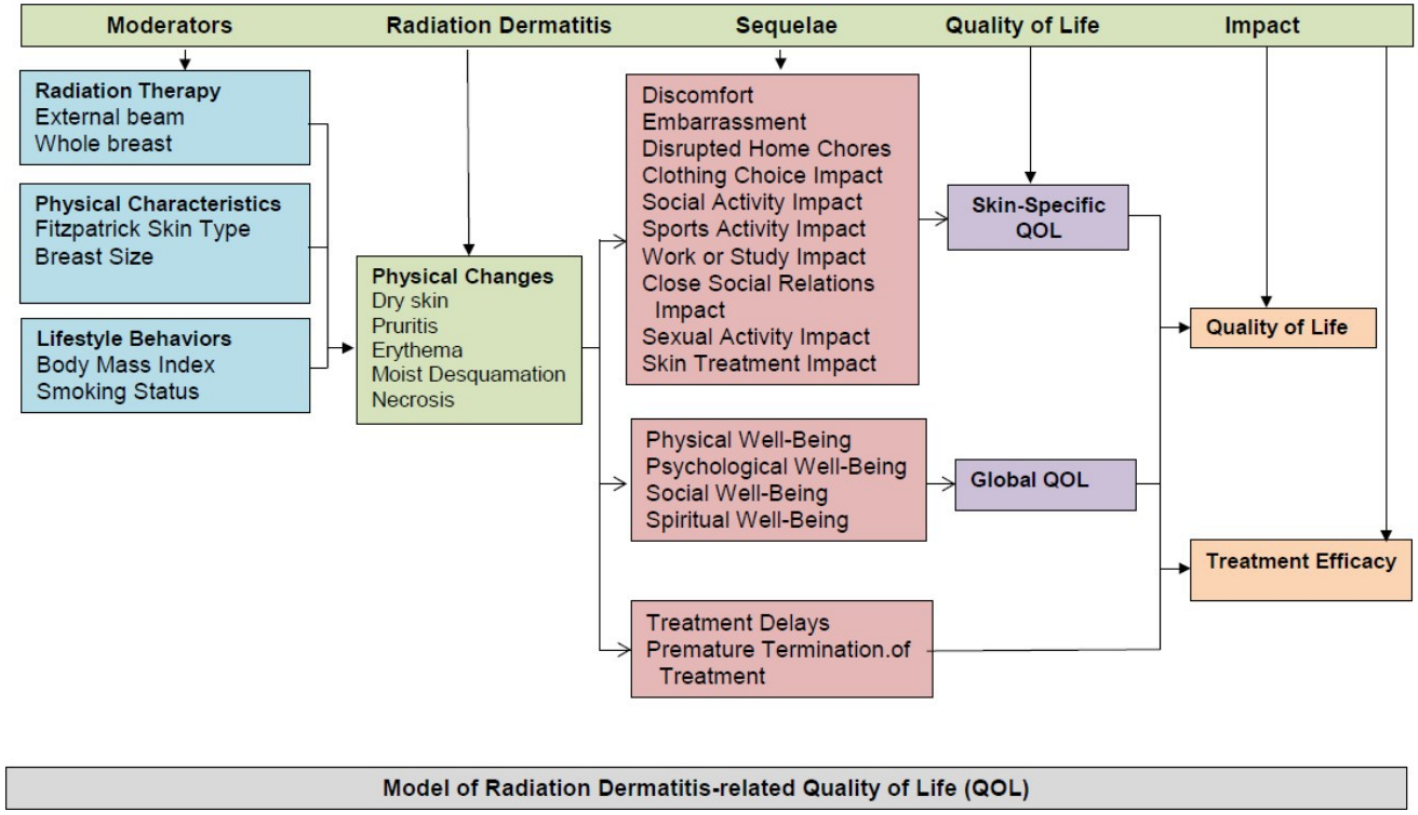

Figure 3.1. Logic model of radiation dermatitis-related quality of life (present study)

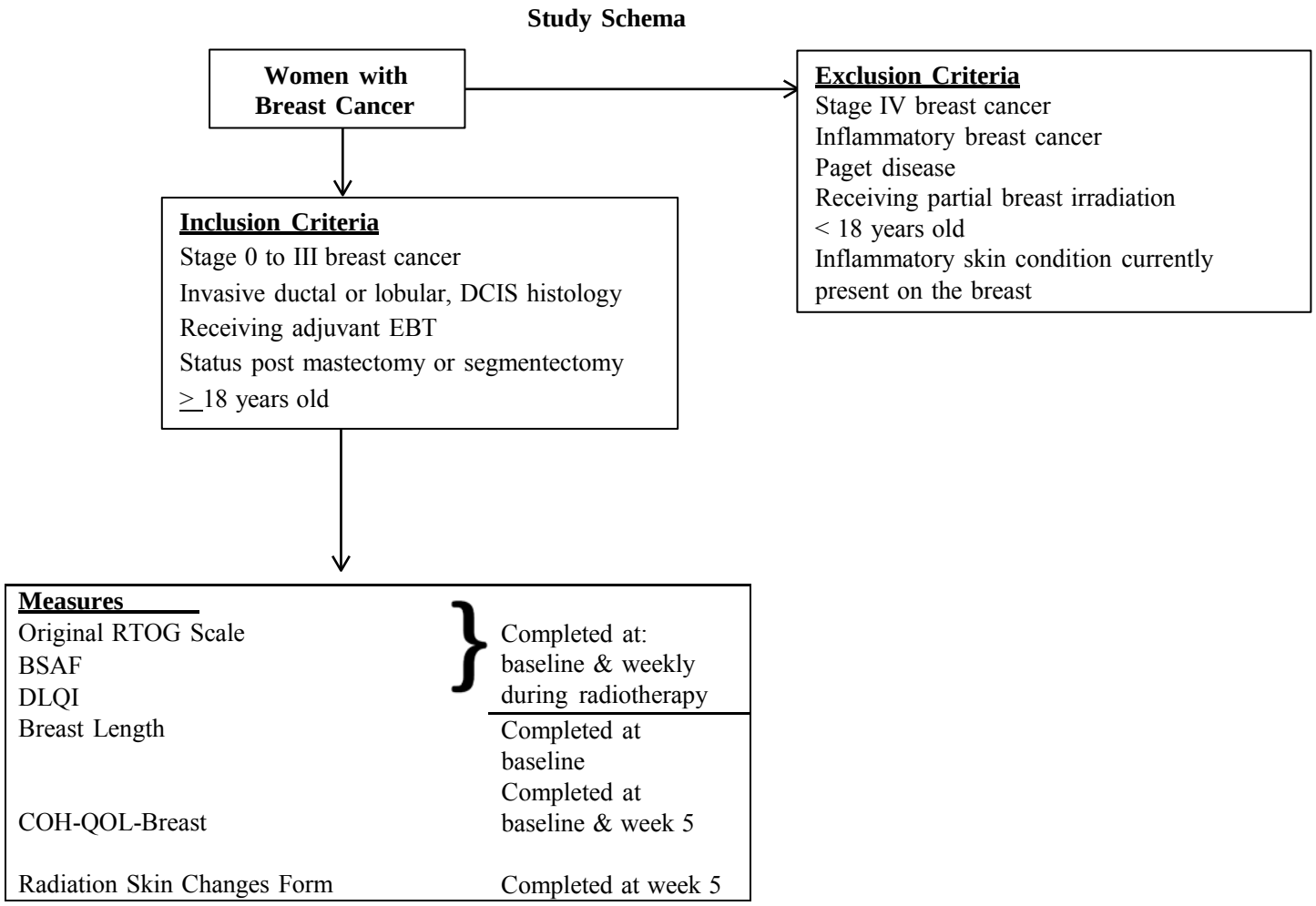

Figure 3.2 Schema for study

	[0]	[1]	[2]	[3]	[4]
SKIN	No change over baseline	Follicular, faint, or dull erythema/epilation/dry/ desquamation/decreased sweating	Tender or bright erythema, patchy moist desquamation/moderate edema	Confluent, moist desquamation other than skin folds, pitting edema	Ulceration, hemorrhage, necrosis

Figure 3-3. RTOG Acute Morbidity Scoring Criteria-Skin

CHAPTER 4

FEASIBILITY AND PILOT STUDY EVALUATING IMPACT OF CLINICIAN-MEASURED BREAST LENGTH ON RADIODERMATITIS AND VALUE OF MULTIPLE LONGITUDINAL SKIN ASSESSMENTS IN THE TREATMENT FIELD

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Abstract

Purpose

We explored the role of clinician-measured breast length and bra cup size in the development of radiodermatitis over time on treatment and the efficacy of using multiple measurements of skin toxicity during radiotherapy as an outcome in a pilot study. The feasibility of measures to be used in a larger future study was assessed then described quantitatively and narratively.

Methods and Materials

We studied women receiving normofractionated or accelerated external radiotherapy provided in the supine position using 3-dimensional conformal techniques at a community cancer center in northwestern Illinois in this descriptive study. Acute skin toxicity was assessed using the RTOG scale in 7 areas within the treatment field across 6 time-points. The total score for the 7 areas was calculated each week. Breast length was measured, used as a variable to describe its role in the development of acute radiodermatitis in the 7 areas within the treatment field, and compared against reported bra cup size. Repeated-measure ANOVAs examined radiodermatitis using maximum skin toxicity and 7 sites in the radiation treatment field over 6 time-points. Kendall's tau correlation was implemented to explore the relationship between study variables.

Results

Forty women (39 non-Hispanic White, 1 Asian) consented to this study. Increase in breast length significantly correlated with increase in maximum RTOG score ($p = .04$); increased RTOG score in the upper medial breast quadrant ($p = .04$), upper lateral

quadrant (p = .02), lower lateral quadrant (p = .02), inframammary fold (p = .001); with increasing BMI (p = .002) and bra cup size (p = .0003). The clinician-measured breast lengths and participant-reported bra cup sizes were discordant. Overall, our study measures and measurements were feasible.

Conclusions

Our results suggest that measuring breast length and multiple areas in the treatment field is feasible and may increase the sensitivity of skin toxicity assessment. Additional larger studies among diverse populations are needed to determine both the clinical significance of the sum of RTOG scores for 7 areas in the radiation treatment field and the utility of multiple individual scores in the treatment field and clinician-measured breast length.

Introduction

Previous studies of radiodermatitis are limited in that they are typically conducted at major medical centers in urban areas. Additional studies are needed in community settings.

Predictors of radiation dermatitis development have been identified over the past two decades of research. The predictors that were consistently associated with radiodermatitis development include breast characteristics, body mass index, smoking, and skin phototype.

The purpose of this study was to explore the role of clinician-measured breast length and participant-reported bra cup size in the development of radiodermatitis over time on treatment and the efficacy of using multiple measurements of skin toxicity in the

treatment as an outcome in a pilot study. Additionally the feasibility of measures to be used in a larger future study was assessed then described.

Breast Characteristics

Large breasts are consistently associated with increased risk of radiodermatitis.[1-3] However, few studies of radiation dermatitis have included breast measurements such as asymmetry and ptosis as variables. Most pairs of breasts are naturally asymmetrical; conversely, bra cups are equal in size implying bra size may not be an optimal metric as a predictor for radiodermatitis. Liu et al.[4] used medical imaging to calculate seven unique measurements of the breasts (i.e., nipple level, nipple to midline distance, inferior mammary fold level, breast width, breast projection, breast volume, and anterior chest wall projection) in 100 Chinese women. They found that 100% of the women had at least one of the seven parameters significantly different between the breast pairs.[4] An investigation by Wood et al.[5] in Australia revealed 80% of the study population wore incorrectly fitting bras. Moreover, bra cup size may not identify the amount of breast ptosis (i.e., drooping). Pendulous breasts increase the surface area in the inframammary fold and causes a bolus effect during radiation therapy and predisposes the woman to radiation dermatitis.[6,7] These issues support the need for a more precise measurement of the breast in research studies when breast size is used to predict an outcome such as radiation dermatitis. Clinician-measured breast length may provide an answer to this need.

Hidevegi et al.[8] measured the torso surface area of 40 healthy women to estimate body surface area in burn victims and found that "for every increase in cup size, the surface area of a woman's anterior trunk increased by a factor of 0.1 relative to her posterior trunk area" (p. 1595). Additionally, these researchers found the pectoral region

may account for 10% of the total body surface area when the bra cup size is greater than or equal to DD.[8] Using a single measurement of skin toxicity in the breast treatment field does not adequately quantify the body surface area impacted by radiodermatitis.

Although there are several scales used to measure radiation dermatitis, each instrument usually employs one global assessment of the breast treatment field to identify the maximum level of skin toxicity. However, there is a precedent for making multiple assessments of skin toxicity.[3,9,10]

Body Mass Index (BMI)

Overweight and obesity are related to increased incidence of breast cancer.[1-3,11] However, they are also known risk factors for the development of radiation dermatitis.[12,13] A BMI $\geq$ 25 is overweight and BMI $\geq$30 is obese.[14]

Smoking

A strong association exists between smoking during radiation therapy and the development of radiation dermatitis.[1,3,15-17] Similarly, Fisher et al.[18] found a history of lifelong tobacco abstinence was associated with a reduction (p = .026) of radiation dermatitis development. Smoking tobacco causes vasoconstriction of the cutaneous vasculature.[19,20] This tobacco-induced vasoconstriction was scientifically measured using thermography, laser doppler flowmetry, plethysmography, videomicroscopy, pulse oximetry, and oxygen electrode.[19]

Skin Phototype

Fitzpatrick devised a system describing skin types according to risk of developing sunburn.[21] The system implements six phototypes that range from “do not tan, burn

easily" to "become darker, do not burn."[22] Ironically, skin that is darkly pigmented and does not burn but becomes darker is the phototype that often suffers the most severe radiation dermatitis.[23,24] These findings suggest the need for additional studies to explore the use of skin phototype instead of race and ethnicity as a potential predictor of radiation dermatitis development.

Nonphysical Sequelae of Radiation Dermatitis

The nonphysical sequelae of radiation dermatitis include treatment delays, early termination of treatment, suffering, and lost contributions to the family and society. Bese et al.[25] found a significant difference ($p = .022$) in the five and ten year locoregional control of breast cancer recurrence in favor of women with treatment interruptions of 0-7 as compared to $\geq$ 8 days.

Feasibility Study

A feasibility study looks at individual components of a scientific investigation and is used to build the foundation of a larger future study[26] On the other hand, a pilot study is the miniature version of a larger future study.[27] The purpose of this study was to examine the feasibility of individual measures for a future study, pilot a collection of measures planned for use in a larger future study, and provide a scientific estimate of the sample size needed for the future study. Our goals were to assess (1) the feasibility of eligibility and exclusion criteria, recruitment, retention, refusal, and adherence; (2) explore the role of clinician-measured breast length and participant-reported bra cup size in the development of radiodermatitis over time on treatment and the efficacy of using multiple measurements of skin toxicity in the treatment field, and (3) calculate effect

sizes needed to estimate required sample sizes for future studies.

Methods and Materials

This article presents a subset of a broader, longitudinal, mixed-methods pilot study on the health-related quality of life of women experiencing radiodermatitis while actively receiving external radiotherapy for breast cancer. The first author served as the study principal investigator (PI) and single rater of measures and outcomes. Each participant served as her own control for the outcomes in this study using repeated measurements.

Setting

The study was completed at a Comprehensive Community Cancer Program in northwestern Illinois. The external treatments were delivered via a Varian Clinac EX linear accelerator using 3-dimensional conformal techniques including stand open field, hard and enhanced dynamic wedges, and irregular surface compensation. All of the patients were treated in the supine position. Thirty-three women received normofractionated (i.e., 180-200 cGy) doses and seven women received accelerated treatment using fractions of 266 cGy.

Feasibility Measurement

Thabane's[28] Table 2—*Reasons for conducting pilot studies* (p. 4) provided a framework for assessing the feasibility of our study. The four domains framing our assessment included process, management, resources, and scientific.

Pilot Measurements

Biometrics

Height and weight were measured at baseline, then the BMI was calculated using the online Centers for Disease Control and Prevention Adult BMI Calculator.[29] Participant-reported bra cup and band size was recorded. The PI measured the length of the affected breast in women who underwent lumpectomy or mastectomy with immediate reconstruction. The contralateral breast was measured in women who underwent mastectomy without reconstruction. The measurement was standardized by using the midclavicular line as a landmark, then measuring the breast length from inframammary fold to nipple in centimeters using a 72" disposable paper measuring tape manufactured by Medline.

Breast Skin Assessment

The maximum skin toxicity in the radiation treatment field was assessed weekly by the PI using the RTOG Acute Radiation Morbidity Scoring Criteria for skin.[30,31] Developed by radiation oncology experts for use in clinical trials with an acute radiodermatitis outcome, the RTOG scale includes four ordinal grades of radiation-induced skin toxicity including "0" no change from baseline; "1" follicular, faint or dull erythema/ epilation/dry desquamation/ decreased sweating; "2" tender or bright erythema, patchy moist desquamation/ moderate edema; "3" confluent, moist desquamatiom other than skin folds, pitting edema; and "4" ulceration, hemorrhage, necrosis.[30,31] The PI also assessed the RTOG score for the upper outer quadrant, upper inner quadrant, lower outer quadrant, lower inner quadrant, and inframammary fold of the breast; axilla, and subclavicular area to represent the surface area affected and to

allow for examination of skin-related quality of life related to specific anatomical sites in the treatment field. The RTOG score for these seven areas was summed to provide a total score that represents surface area and severity of breast radiodermatitis.

Skin Phototype

The skin phototype was determined by the PI during a short interview with the participant. The potential ratings included: type I—always burns, never tans, type II—always burns easily, tans minimally, type III—burns moderately, tans uniformly, type IV—burns minimally, always tans well, type V—rarely burns, tans profusely, and type VI—never burns.[22]

Radiation Treatment

The radiation treatment plan (i.e., normofractionated, accelerated) was recorded at the start of the study. The cumulative radiation dose, energy, fraction number, and use of a breast immobilizer or bolus pad were recorded weekly.

Sample Size

Recommended sample size for pilot studies is a contentious topic and suggestions have ranged from 12 subjects per arm to totals of 30 to 50 subjects.[32-34] We sought to have sufficient power to accurately detect significant differences in our larger pilot study looking at the impact of radiodermatitis on skin-related quality of life. Lacking an a priori estimate of effect, a sensitivity analysis was conducted using G*Power version 3.1.9.1,[35] with a sample size of 40 participants in one group, .10 alpha level of significance, power of .80, epsilon of 1.0, correlation of .50, and six repeated measurements. Using these parameters, we could expect to detect an effect size of .15 which is a small effect size

using Cohen's criteria.[36] Since we planned to conduct a descriptive feasibility and pilot study, a slightly relaxed level of significance was acceptable in that it help us avoid missing small but clinically significant differences.

Statistical Methods

The IBM[37] Statistical Package for the Social Sciences Statistics for Windows Version 21.0 was used to create a database and analyze the quantitative data collected. Means, standard deviations, and ranges were calculated for continuous data; while frequencies and ranges were determined for categorical data. A one-way within-subjects repeated measures ANOVA was conducted to compare skin toxicity grade of the breast using the RTOG scoring system, to compare skin toxicity grade of the breast using the RTOG scoring system by each individual area in the radiation treatment field, and the total of all scores at baseline and weeks 1, 2, 3, 4, and 5 on external radiation therapy.

Kendall's tau is a nonparametric correlation used instead of a Spearman Rho correlation when the sample size is small and there are tied ranked scores (e.g., RTOG scores by breast site).[38] Therefore, a Kendall's tau correlation was performed to measure the relationship between factors and the severity of radiation dermatitis at five weeks on external radiotherapy of the breast since our sample was small.

Results

Sample

A purposive sample of 41 English-speaking adult women with stage 0-III breast cancer identified as candidates for external beam radiotherapy were accrued to the study from May 2014 through May 2015. One participant withdrew from the study during the

first week. All of the remaining 40 participants were followed from baseline to completion of radiotherapy and completed all study measures.

One participant had a history of vitiligo. Her depigmented skin did not develop radiodermatitis. Her normally pigmented skin reacted similarly to other study participants' skin. Another participant had a history of polycystic ovary syndrome. The skin over multiple areas of her body outside of the treatment field was hyperpigmented. This participant also had very large breasts, developed grade 3 skin toxicity in the inframammary fold, and required a 2-day treatment break. A third participant with very large breasts developed grade 3 skin toxicity in the inframammary fold and axilla. She required a 9-day treatment break including 4 weekend days. Her skin was examined at the predetermined weekly study time points and additional times when she came to the cancer center for skin checks. The reported results focus on baseline and five weekly observations since seven participants received accelerated treatments and were unavailable for follow-up observations. Additional information about the participants is provided in Table 4.1.

Feasibility

Field notes on feasibility and best practices were documented throughout the study. Rates on recruitment, refusal, retention, withdrawal, study measures, and measurements were calculated. The results of our assessment of feasibility are presented in Table 4.2.

Pilot Study Outcomes

A comparison of participant-reported bra cup size and clinician-measured breast length is presented in Table 4.3. Participant-reported bra cup size, a new measurement, was compared to measured breast length, the current standard measure. Bra cup sizes and measured breast lengths were discordant in this study. For example, a woman with a breast length of 5 cm reported wearing a C cup ,while another woman with a 6.5 cm breast length reported wearing an AA-sized bra cup. Women with 10.5 cm breast lengths reported wearing a D, DD, or DDD-sized bra cup.

A one-way within-subjects repeated measures ANOVA was conducted to compare skin toxicity grade of the breast using the RTOG scoring system at baseline and weeks 1, 2, 3, 4, and 5 on external radiation therapy. The means and standard deviations are presented in Table 4.4. The maximum skin toxicity score significantly increased with time on radiation treatment, Wilk's Lambda = .05 F (5, 35) = 132.07, p <.00001, multivariate partial eta squared = 0.95. Overall, 20% of the participants experienced grade 1, 75% had grade 2, and 5% suffered grade 3 skin toxicity at five weeks on treatment. A one-way within-subjects repeated measures ANOVA was conducted to compare skin toxicity grade of the breast using the RTOG scoring system for each individual area in the radiation treatment field and the total of all scores at baseline and weeks 1, 2, 3, 4, and 5 on external radiation therapy. The means, standard deviations, Wilk's Lambda, F statistic, degrees of freedom, significance level, and eta squared are presented in Table 4.5. Skin toxicity significantly increased with time on radiation treatment in every site in the radiation treatment field. There was a significant effect size (η^2) for time in each area in the treatment field, ranging from η^2 .60 to .89 with the

smallest effect in the subclavicular area and the largest effect in the axilla. The effect of time on the total toxicity score for all areas was $\eta^2 = .90$, $p < .001$.

The relationship between factors and the severity of radiation dermatitis at five weeks on external radiotherapy of the breast was measured using Kendall's tau correlation. The results are presented in Table 4.6. As expected, there were a number of significant correlations between severe radiodermatitis in one area and another area of the breast. For example, if radiation dermatitis increased in one breast quadrant, it significantly increased in all of the other quadrants, supporting the need for multiple measurements of skin toxicity. Radiodermatitis severity in the inframammary fold was significantly associated with increased severity in the lower, but not upper breast quadrants.

Race and ethnicity did not have any significant correlations in our nearly all White study population. However, as skin phototype (i.e., sunburn resistance) increased, radiodermatitis in the inframammary fold also significantly increased ($r = .34$, $p = .02$). This suggests that skin phototype might be able to discriminate between skin types among individuals of the same race.

With regard to biometrics, as body mass index increased skin toxicity significantly increased in the inframammary fold ($r = .32$, $p = .01$) and axilla ($r = .26$, $p = .05$). An increase in bra cup size correlated with an increase in maximum RTOG score at five weeks on radiotherapy ($r = .29$, $p = .04$), upper medial breast quadrant ($r = .29$, $p = .04$), lower lateral quadrant ($r = .30$, $p = .02$), inframammary fold ($r = .41$, $p = .004$), and BMI ($r = .42$, $p = .005$). Breast length was associated with an increase in in RTOG score ($r = .28$, $p = .04$), upper medial breast quadrant ($r = .28$, $p = .04$), upper lateral quadrant (r

= .30, p = .02), lower lateral quadrant (r = .30, p = .02); and a highly significant association with inframammary fold (r = .45, p = .001), increasing BMI (r = .41, p = .002), and bra cup size (r = .57, p = .0003). Overall, breast length had a greater number of highly significant correlations. This suggests that breast length may have a stronger relationship with radiodermatitis severity as compared to bra cup size.

Discussion

In this study, we explored the role of clinician-measured breast length and bra cup size in the development of radiodermatitis over time on treatment and the efficacy of using multiple measurements of skin toxicity during radiotherapy.

Feasibility

We first studied the feasibility of enrolling women with breast cancer into a longitudinal study with weekly assessments of skin toxicity. The women living in our community setting were committed to finishing all of the measurements if they elected study participation as evidenced by a 98% retention and 18% refusal rate. Our proposed measures were feasible in the current study except for the plan to examine the development of radiodermatitis by predetermined cumulative radiation doses. Measuring radiodermatitis at specific cumulative doses would help control for differences between participants that occurs with measurements documented by week on radiotherapy. For example, participants frequently start and complete radiotherapy on various days of the week and different doses may be prescribed. However, we were not able to measure skin toxicity by specific cumulative doses related to the PI's employment obligations.

Piloted Measures

We piloted two measures that could improve the ability to predict or measure skin toxicity. Accurately identifying risk factors for breast radiodermatitis is important for studies of measures that may prevent or manage that toxicity.

The current study demonstrated a number of significant findings. As expected, the maximum skin toxicity (i.e., RTOG) score significantly increased with time on radiotherapy and the mean score at five weeks on radiotherapy was 1.85. Moreover, skin toxicity significantly increased with time on radiotherapy in every site in the radiation treatment field. More importantly, by implementing multiple assessments of skin toxicity, our results showed a mean RTOG score of more than 1.0 in all areas of the treatment field, 1.58 in the inframammary fold, and 1.60 in the axilla at five weeks on radiotherapy. A grade 1 acute skin toxicity may include dry desquamation, while grade 2 may include patchy moist desquamation and is considered a moderate to severe toxicity.[39]

The mean of the summed RTOG scores for all seven sites in the treatment field was 8.85, much higher than a single measurement of the maximum skin toxicity. Assessing dermatitis in multiple areas within the radiation treatment field can be performed quickly when the data is inputted into a standardized form. While the clinical significance of the summed RTOG scores remains to be determined, these multiple measurements may provide increased sensitivity to small but clinically significant subjective changes in radiation dermatitis during studies to test potential interventions. Additionally, use of multiple measurements can allow for a scientific comparison of the efficacy of interventions in one site in the treatment field versus another site. For example, an intervention may work well on a quadrant of the breast but not as well in the

inframammary fold.

We proposed the concept of clinician-measured breast length for this feasibility study because studies have shown that bra cup size is not a reliable proxy for actual breast size. As illustrated in Table 4.3, participant-reported bra cup size was discordant with clinician-measured breast length, which is a more scientific alternative to participant-reported bra cup size. Breast length was significantly positively correlated with radiodermatitis in the inframammary fold and upper medial, upper lateral, and lower lateral breast quadrants in this study. Similarly, Porock et al.[1] found bra cup size greater than size C predicted an RTOG skin toxicity score of 2 or higher in the inframammary fold, upper outer quadrant, upper inner quadrant, lower outer quadrant, and lower inner quadrant of the breast radiotherapy treatment field. Pires, Segreto, and Segreto[40] measured breast height (i.e., distance from the chest wall to nipple measured on a contour plan), and found that each centimeter of increased height increased the chance of developing grade 3 skin toxicity by 2.61 fold. Overall, these findings support the importance of breast size as a risk factor for radiodermatitis.

Measuring the breast length takes only a few seconds and is not costly disposable measuring tapes are inexpensive (e.g., 15 cents each in our study) and the measurement can be completed by a registered nurse or trained research associate. Conversely, breast volume calculation by a radiation oncologist or medical physicist on a contour plan is a more expensive alternative to clinician-measured breast length. To provide a context, Caruso, Guillot, Nguyen, and Greenway[41] compared the cost of using a manual measurement of breast volume (i.e, Grossman Roudner breast-measuring device, breast casting) against medical resonance imaging (MRI) to objectively estimate increase in

breast size after application of topical compounds as an alternative to breast augmentation surgery. Use of MRI was 373 to 33,500 times more expensive than the manual method of measuring breast volume.

Clinician-measured breast length may prove an effective predictor of radiodermatitis instead of, or in addition to, participant-reported bra cup size. However, evidence regarding the comparative effectiveness of clinician-measured breast length, a new measure, versus participant- or client-reported bra cup size, the current standard, is still needed.[42]

Strengths and Limitations

There are a number of strengths of this study. For example, accrual goals were met. There was only one rater of skin toxicity eliminating the issue of interrater reliability. However, threats to intrarater reliability include fatigue, time of day, attention.[43] Each woman served as her own control eliminating between subjects variance. We tested and reported the feasibility of our measures planned for use in future studies.

Study limitations include a small sample size with limited diversity. We hoped to examine skin toxicity by severity and site using cumulative radiation dose as the factor. It was not feasible to track the participants throughout the course of radiation therapy to collect skin toxicity by specified cumulative radiation dosages (i.e., 900 cGy, 1800 cGy, etc.).

Conclusions

This pilot and feasibility project enabled us to identify several recommendations that will be important in similar future research studies. For example, performing assessments on Mondays allowed for follow-up on Tuesday through Friday to collect missing information for a given week. Ideally, future investigators or research staff should be onsite on a daily basis to facilitate recruitment and collection of time-sensitive data. Our data collection form for seven areas in the breast radiation treatment field worked well but might be improved by adding an image of the posterior surface of the chest. Creating a form with an image of mastectomy without reconstruction (i.e., chest wall) would also aid in mapping radiodermatitis.

Additional studies are needed to determine the clinical significance of the total RTOG score for all areas in the radiation treatment field. The utility of clinician-measured breast length and multiple measurements of skin toxicity in the treatment field must be tested in larger studies and more diverse populations. However, it was feasible to complete these measurements in a study set at a community cancer program.

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Table 4.1
Sample Characteristics (n = 40)

Age in years		
Mean (Range)	59 (40-82)	
SD	11.63	
BMI (kg/m^2)		
Mean (Range)	29 (18.0 -52.9)	
SD	8.04	
Nipple-to-fold breast length in cm		
Mean (Range)	9.20 (5-19)	
SD	2.99	
	Frequency (%)	
Bra cup size		
AA	1	(2.5)
A	2	(5)
B	6	(14)
C	16	(40)
D	7	(17.5)
DD	4	(10)
DDD	1	(2.5)
J	2	(5)
Does not wear a bra	1	(2.5)
Bra band size		
Median	36	(32-44)
Smoking status		
Current smoker	3	(7.5)
Previous smoker	19	(47.5)
Never smoked	18	(45)
Race/Ethnicity		
Non-Hispanic White	39	(97.5)
Asian	1	(2.5)
Skin phototype		
I	8	(20)
II	11	(27.5)
III	11	(27.5)
IV	5	(12.5)
V	5	(12.5)
VI	0	(0)
Stage*		
0 (Tis)	7	(17)
I	7	(17)
IIa	15	(36)
IIb	3	(7)
IIIa	4	(10)
IIIb	2	(5)
IIIc	2	(5)
Grade		
1	6	(15)
2	19	(47.5)
3	15	(37.5)
Tumor Histology		
Ductal	28	(70.0)
Lobular	5	(12.5)
DCIS	7	(17.5)
Receptor status		
ER positive	33	(82.5)
PR positive	30	(75)
HER2 positive	9	(22.5)
Surgery		
Lumpectomy	28	(70.0)
Mastectomy with reconstruction	5	(12.5)
Mastectomy without reconstruction	6	(15)
None	1	(2.5)
Systemic therapy (yes)		
Chemotherapy	22	(55)
Hormone therapy	0	(0)
Trastuzumab	6	(15)

*Values are rounded to the nearest whole number

Table 4.2

Assessment of Feasibility

Process	**Findings/Recommendations**
Recruitment	Recruitment was most successful on the consultation day, moderately successful at the simulation visit, and least successful just prior to treatment on the first day of therapy. It took 13 months to recruit our participants.
What was the refusal rate?	18% (9 of 50 potential participants declined participation)
Can the refusal rate be decreased without coercion?	The most frequent reason for refusal was "overwhelmed right now." One woman perceived participation in any study as highly experimental and "beyond imagination."
What was the retention rate?	98% (Only 1 of 41 participants who consented withdrew)
Can the retention rate be improved?	All participants who remained in the study beyond the baseline time point completed all of the measures
Eligibility criteria:	
Are there any problems with the eligibility criteria?	Recommend including women with inflammatory breast cancer who are post-mastectomy Recommend including males and transgender females with breast cancer Recommend including individuals with certain conditions affecting skin pigmentation such vitiligo and polycystic ovary syndrome
Measures	
Are there any problems with the instruments?	The income range on the demographics form should extend higher than $75,000 per year Create a breast skin assessment form with a mastectomy image Consider adding an image of a back on the breast skin assessment form RTOG Acute Radiation Morbidity Scoring Criteria does not clearly delineate between erythema and patchy moist desquamation
Resources	**Findings/Recommendations**
Determine capacity and identify best practices	Assessing for skin toxicity in the treatment vault during set-up for treatment prevented the need to use an exam room and saved the participant from needing to undress for the study Investigator having a pre-existing working relationship with the radiation oncology team enhances trust and cooperation Conducting study assessments every Monday worked well in a department operating Monday-Friday. This allows 4 days in a row to capture any missed assessments since many radiation oncology departments operate on a Monday through Friday basis On rare occasions, patients would request a one-time change in appointment time. The PI was not informed of these changes since she was not employed at the cancer center and this led to missed assessments requiring extra trips to the cancer center.
Does the center adhere to promises?	No problems identified

Table 4.2 Continued

Management	**Findings/Recommendations**
What qualifications are needed by the PI?	Researcher needs to be familiar with and work in radiation oncology department, and have dedicated time for the study (e.g., all study measures, data management).
Are there improvements needed to enhance management of the study?	Scannable data forms would likely enhance data accuracy and save time
Scientific	**Findings/Recommendations**
Can effect sizes be calculated and to which populations do they apply?	Calculating effect sizes (ES) to inform future power analyses is helpful. Care must be taken to avoid over-relying on the ES from a study that is not identical to your own.

Table 4.3**.**

Comparison of Participant-reported Bra Cup Size and Clinician-measured Breast Length

Bra Cup Size	**n**	**Breast Length in cm (range)**
AA	1	6.5
A	2	5.0-7.0
B	6	6.0-8.0
C	16	5.0-12.5
D	7	7.5-10.5
DD	4	10.5-19
DDD	1	10.5
J	2	14.0-15.0
Does not wear a bra	1	10.5

Table 4.4.

*Descriptive Statistics for Radiation-induced Skin Maximum Toxicity of the Breast at Baseline and Weeks 1 to 5 on Radiotherapy**

Time Period	n	M	SD
Baseline (before RT)	40	.00	.00
Week 1 on RT	40	.10	.30
Week 2 on RT	40	.60	.67
Week 3 on RT	40	1.08	.69
Week 4 on RT	40	1.45	.55
Week 5 on RT	40	1.85	.48

Abbreviations: RT = Radiotherapy, *n* = number of participants assessed, M = mean, SD = standard deviation

*The RTOG Acute Radiation Morbidity Scoring Criteria-Skin was used to measure maximum skin toxicity. The ratings range from "0" no change over baseline; "2" tender or bright erythema, patchy moist desquamation/ moderate edema; "3" confluent, moist desquamatiom other than skin folds, pitting edema; and "4" ulceration, hemorrhage, necrosis.

Table 4.5.

Summary Table for Within-subjects Repeated Measures Analysis of Variance of Radiodermatitis of the Breast by Site in the Treatment Field

Time	M	SD	Wilkes λ	F	DF*	p	η^2
Upper Medial Quadrant			.23	23.90	(5,35)	<.001	.77
Baseline	.00	.00					
Week 1	.03	.16					
Week 2	.13	.40					
Week 3	.50	.68					
Week 4	.68	.73					
Week 5	1.18	.68					
Upper Lateral Quadrant			.16	35.72	(5,35)	<.001	.84
Baseline	.00	.00					
Week 1	.05	.22					
Week 2	.25	.54					
Week 3	.65	.70					
Week 4	.70	.69					
Week 5	1.23	.62					
Lower Medial Quadrant			.18	32.87	(5,35)	<.001	.82
Baseline	.00	.00					
Week 1	.03	.16					
Week 2	.23	.48					
Week 3	.63	.67					
Week 4	.80	.79					
Week 5	1.13	.61					
Lower Lateral Quadrant			.16	37.07	(5.35)	<.001	.84
Baseline	.00	.00					
Week 1	.08	.27					
Week 2	.15	.36					
Week 3	.73	.68					
Week 4	.95	.78					
Week 5	1.20	.61					

Table 4.5 Continued

Time	M	SD	Wilkes λ	F	DF*	p	η^2
Inframammary Fold							
Baseline	.00	.00	.12	66.97	(4,35)	<.001	.88
Week 1	.00	.00					
Week 2	.23	.48					
Week 3	.78	.66					
Week 4	1.25	.67					
Week 5	1.58	.64					
Axilla							
Baseline	.00	.00	.11	56.57	(5,35)	<.001	.89
Week 1	.03	.16					
Week 2	.15	.36					
Week 3	.43	.71					
Week 4	.93	.69					
Week 5	1.60	.59					
Subclavicular Area							
Baseline	.00	.00	.40	10.60	(5,35)	<.001	.60
Week 1	.03	.16					
Week 2	.28	.55					
Week 3	.48	.75					
Week 4	.65	.74					
Week 5	1.00	.85					
Total for all Sites			.10	65.22	(5,35)	<.001	.90
Baseline	.00	.00					
Week 1	.23	.86					
Week 2	1.40	2.04					
Week 3	4.08	3.34					
Week 4	5.95	3.65					
Week 5	8.85	3.08					

Abbreviations: M = mean, *SD* = standard deviation, DF = degrees of freedom (hypotheses, error), n^2 = eta squared

Table 4.6.

Variables Related to the Severity of Radiation Dermatitis at Week 5 among Women Receiving Breast Radiotherapy

	Measure	1	2	3	4	5	6	7	8	9	10	11	12
1	RTOG Score	—											
2	Upper Medial	.45†	—										
3	Upper Lateral	.37*	.38†	—									
4	Lower Medial	.39†	.66†	.55†	—								
5	Lower Lateral	.43†	.53†	.57†	.43†	—							
6	Inframam Fold	.65†	.21	.22	.53†	.48†	—						
7	Axilla	.61†	.49†	.26	.57†	.44†	.53†	—					
8	Sub-clavicular	.18	.08	.05	.77†	.13	.12	.26	—				
9	Skin Type	.18	.18	.18	.19	.09	.34*	.21	-.02	—			
10	BMI	.15	.15	.13	.13	.22	.32*	.26*	-.05	-.06	—		
11	Bra Cup Size	.29*	.29*	.19	.19	.31*	.41†	.22	-.16	.07	.42†	—	
12	Breast Length	.28*	.28*	.30*	.23	.30*	.45†	.16	-.01	.18	.41†	.57†	—

Abbreviations: Inframam Fold = inframammary fold, *Correlation is significant at the 0.05 level (2-tailed), †Correlation is significant at the 0.01 level (2-tailed).

CHAPTER 5

DOES THE DERMATOLOGY LIFE QUALITY INDEX (DLQI) ADEQUATELY REFLECT THE SYMPTOMS OF WOMEN EXPERIENCING BREAST RADIODERMATITIS?

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Abstract

Purpose

The purpose of this pilot study was to begin the validation process for using the Dermatology Life Quality Index (DLQI) for radiodermatitis of the breast.

Methods

Participants completed the DLQI instrument weekly while receiving external radiotherapy of the female breast. At week five on treatment, 31 (78%) participants provided narrative feedback on how each DLQI item impacted her life. Agreement between the DLQI numerical ratings and the narrative feedback was assessed. Construct validity was estimated using principal component analysis (PCA). Reliability of the DLQI was assessed using Cronbach's alpha.

Results

Agreement between DLQI ratings and narratives ranged from .71 to .98. The DLQI work and study subscale was removed from our analyses because the variance was zero. PCA supported the inclusion of all of the remaining subscales. The remaining DLQI subscales demonstrated good internal consistency, $\alpha = .84$.

Conclusions

The results of our examination of the DLQI when used for breast radiodermatitis are promising. Additional larger studies among more diverse populations are needed.

Introduction

A majority of women receiving external beam radiotherapy for breast cancer experiences radiation skin changes.[1] The current standard of care in radiation oncology is to describe the physical attributes of radiodermatitis as a skin toxicity. Although this is important, it does not address the patient's personal experience. The results of previous studies have demonstrated that women receiving external beam radiation therapy for breast cancer experience significant alterations in health-related quality of life (QOL). For example, Pignol et al.[2] found a highly significant correlation between the development of moist desquamation, an increase in reported breast symptoms ($p = .0028$) and pain score ($p < .0001$). Women actively receiving external beam radiation therapy for breast cancer in a study by Miller et al.[3] reported experiencing itching, burning, stinging, pain, irritation, embarrassment, depression, decreased social interaction, and diminished ability to show affection. The profound effect radiation dermatitis has on quality of life causes some women to withdraw from treatment.[4] Radiation dermatitis is related to a constellation of physical factors such as radiation-induced skin changes, inflammatory responses, and genetic endowment.[5,6] Further, these physical factors directly impact quality of life among women receiving external beam radiotherapy for invasive breast cancer. Schnur et al.[7] found a relationship between season of the year and amount of skin bother.

To help remedy the dilemma of radiodermatitis impact on quality of life, a scientifically and independently validated instrument to measure skin-related quality of life among patients receiving radiation therapy is needed. The Dermatology Life Quality Index (DLQI) is an instrument well-validated for frequent clinic use in a number of

dermatologic conditions including eczema.[8] Eczema is somewhat similar to radiation dermatitis since it causes itching, erythema, edema, and moist desquamation.[9.10] However, the DLQI has not been formally validated for use in radiodermatitis. We sought to begin the validation process for using the DLQI for radiodermatitis in our pilot study**.**

Methods

This report describes a subset of a larger study. A purposive sample of women about to undergo external breast radiotherapy was recruited at a Midwestern cancer program in a community setting.

Baseline measures were completed, then the women were followed throughout radiotherapy. Skin-related quality of life data were collected two survey instruments (i.e., DLQI, radiation skin changes form). Participants completed the DLQI at baseline and each week while on radiotherapy during the main study. At the fifth week on radiotherapy, the participants were asked to provide written feedback on how the Dermatology Life Quality Index (DLQI) items impacted their lives. This feedback was written on the radiation skin changes form.

Validity Testing

There are many components in the process of validating an instrument.[11] Each process measures a different aspect of the instrument's strengths or weaknesses. We estimated the concurrent, content, construct validity, and reliability of the DLQI among women with breast radiodermatitis in our pilot study.

Concurrent Validity and Informant Agreement

Concurrent validity focuses on the extent to which a measure such as the DLQI adequately reflects the individual's perspective on a criterion.[12] We measured the concurrent validity of the DLQI by assessing the agreement of participant informant's responses on the DLQI and their narrative responses to a survey about the DLQI, both at five weeks on radiotherapy. Informant agreement was measured at five weeks on treatment when skin toxicity begins to peak. An extra copy of the DLQI and the only copy of the radiation skin changes form were given to the participant. Each woman was instructed to look at the extra copy of DLQI. Next, participants were invited to write narratives about how each item on the DLQI impact their life. Thirty-one (78%) of the 40 participants provided narratives. The principal investigator (PI) abstracted the week five DLQI responses and the narratives on impact. The data were entered into a form with a column for the ordinal score on the DLQI (i.e., very much, a lot, a little, not at all), a column for a verbatim copy of the narrative, and a column for researcher rated level of agreement. Three researchers jointly coded the agreement score (i.e., agree, disagree) for each DLQI participant rating and narrative for the first participant. Subsequently, each researcher coded her perceived level of agreement for the remaining participant responses independently. The PI combined the agreement ratings by each researcher into one master document. The document was shared with each researcher, the agreement ratings were discussed and consensus formed for items on which the agreement ratings did not originally agree. Percent agreement was calculated by dividing the total number of participant responses for each DLQI item by the number of paired responses where the participant's DLQI rating was congruent with her narrative response.

Content Validity

Content validity focuses on whether the instrument represents the domain of interest.[12] In this study, it was assessed by soliciting feedback on the DLQI from expert 12 radiation oncology nurses at a chapter meeting of the Oncology Nursing Society. A hard copy of the DLQI was given to each nurse. The nurse was instructed to read the items on the DLQI and provide written feedback on the items.

Construct Validity

Construct validity focuses on the extent that items on a measure such as the DLQI are consistent with the concept of interest.[12] It was assessed using principal component analysis (PCA) of the DLQI subscales. A variety of participant per factor ratios are suggested in the professional literature, ranging from 3 to 15 participants for each factor.[13-17] We had 40 participants and five subscales yielding a ratio of 8:1. Our sample size adequacy was also estimated post hoc by examining the Kaiser-Meyer-Olkin (KMO) statistic and communalities after extraction, both with values greater than 0.5 if the sample size is adequate.[18] The work and study subscale was removed during analysis from the PCA because the variance in participant responses was zero for this subscale.

Reliability

The reliability of the DLQI subscales was assessed using a Cronbach's alpha analysis and examining the interitem correlations. An alpha of 0.7 or higher and inter-item correlation of 0.3 or greater was considered acceptable.[18] Again, the work and study subscale was removed from the analysis since the variance was zero.

Statistical Analyses

The IBM Statistical Package for the Social Sciences (SPSS) Statistics for Windows Version 21.0 was used to analyze our quantitative data.[19] Principal component analysis and direct oblimin rotation were used to examine the loading of the DLQI subscales. Cronbach's alpha was used to examine the internal consistency of the DLQI.

Human Research Subjects Protection

This study was approved by the University of Utah Institution Review Board (UIRB). A reliance agreement was created between the UIRB and the health care system affiliated with the cancer program. Each woman provided her consent to participate in the study. Only the principal investigator had access to participants' personal health information. A unique participant identification number was assigned to promote anonymity and confidentiality with other investigators. This number was used to link all study documents for each participant

Results

Sample of Participants with Breast Cancer

Thirty-one of the 40 participants in the main study provided usable narrative responses about the DLQI items. All 40 participants were female with stage 0 to III breast cancer. They ranged in age from 40 to 82 years with a mean age of 58 years. The typical participant was non-Hispanic White (97%), had some level of college education (74%), worked in a professional occupation (42%), earned more than $75,000 annually (45%), was normal weight (39%) or obese (39%), and did not currently smoke (94%). See Table 4.1 in Chapter 4 for additional details.

Validity

Concurrent Validity/Informant Agreement

The percent of agreement between participant ranked responses on the DLQI and narrative responses on the radiation skin changes form ranged from 71% to 98%. See Table 5.1. There is no established standard for acceptable informant agreement. However, Graham, Milanowski, and Miller[20] suggest using a range of 75% to 90% absolute agreement as a measure of interrater agreement. Our results closely parallel that range.

The first item on the DLQI inquires about three sensations (i.e, pruritis, pain, stinging) and had the lowest level of agreement. The respondent needed to mention these three sensations to meet the requirements for agreement. The item that focuses on sports had the highest level of agreement. However, most participants responded that their skin did not impact their ability to do any sports because they did not frequently engage in sporting activities.

Content Validity

The radiation oncology nurses did not recommend the addition or deletion of any DLQI items. They suggested a few minor word changes. For example, "not relevant" might be changed to "does not apply." We found the content validity of the DLQI sufficient based on radiation oncology nurse expert opinions.

Construct Validity

Our KMO statistic was .68 and the communalities ranged from .68 to .92, indicating a sufficient sample size to complete a PCA [18]. Bartlett's test of sphericity $X^2(10) = 111.51$, $p < .001$ indicating the correlations between items were sufficiently

large for PCA. Correlations between the DLQI subscales were calculated and were greater than or equal to .3. See Table 5.2 for additional information. All of the subscales focused on skin-related QOL and were likely correlated. Therefore, a direct oblimin rotation was implemented.[17] The rotated DLQI subscales, sans the work and study subscale, loaded exclusively on one of two components that together explained 83% of the total variance in the analysis, supporting the retention of these subscales. Subscales that clustered on component one include daily activities, leisure, and personal relationships. Subscales that clustered on component two include symptoms and feelings and treatment.

Reliability

The work and study subscale was removed from analysis because the variance was zero. The DLQI remaining subscales demonstrated good internal consistency, $\alpha = .84$ and were worthy of retention. The greatest increase in alpha would come from deleting the treatment subscale. However, removal of this subscale would improve alpha by only .001.

Discussion

No skin-related quality of life instruments independently validated for use in radiation dermatitis were found. As a result, we remain unable to effectively assess the usefulness of topical agents that could decrease suffering, prevent treatment delays or early termination, and improve quality of life for thousands of breast cancer patients. By improving our approach to the assessment of radiation dermatitis and quality of life experienced during this toxicity, we may determine the best methods to prevent and treat

this problem. One potential solution includes using a quality of life instrument specifically designed for skin conditions (i.e., the Dermatology Quality of Life Index) to improve assessment of patient perception of quality of life during the presence of radiation dermatitis. We sought to begin validity and reliability assessment of the DLQI when used to measure skin-related QOL among women experiencing breast radiodermatitis in this pilot study. The DLQI's performance was not perfect, but was acceptable in our pilot study. Further studies are needed to continue the validation of the DLQI for use in breast cancer radiodermatitis.

The overall validity and reliability of the DLQI in our pilot study was good. The percent informant agreement between the DLQI ratings and narrative comments was respectable, ranging from 71 to 98%. Upon assessing the content validity of the DLQI, radiation oncology nurses suggested a few small changes in the wording of the DLQI. However, changing the DLQI would alter its established reliability and validity.[21] Additionally, this instrument is copyrighted and its authors will not permit changes.[22] The variance between our participants on the DLQI work and study subscale was zero and was removed from our statistical analyses. An estimate of construct validity using PCA with a direct oblimin rotation supported the remaining DLQI subscales. The reliability of the remaining subscales demonstrated good internal consistency with $\alpha = .84$. Similarly, the creators of the DLQI reported a Cronbach's alpha of 0.83 when used for dermatologic conditions.[6]

Seasonality, the predictable effects of calendar-related fluctuations in weather condition (e.g., cold weather during winter, hot weather during summer)[23] influenced some participant responses on the DLQI in our study. For example, women who

participated during summer months commented about needing to cover up and avoid sun exposure to radiated areas. Embarrassment was an issue because summer clothes are more revealing than winter clothes. Conversely, winter participants commented that clothing was not an issue because everyone is bundled up. Schnur et al.[7] found similar findings in a study of breast radiodermatitis; in addition to avoiding sun exposure and covering skin changes from view, their study participants reported issues with body odor related to radiodermatitis being an issue during the summer. Seasonality also impacted our participant's responses to the question about sports. Women that liked to golf were bothered if receiving treatment during the summer, but not if treatment was scheduled in the winter. These findings suggest that the results studies focusing on skin-related QOL may be influenced by the season when data are collected.

Strengths and Limitations

One strength of this study is that it can serve as a pilot for future, larger studies. Our sample size was modest, yet statistical testing for adequacy of sample size suggests it was large enough for a pilot study. Caution must be taken regarding applying our results to other populations with greater diversity and living outside of community settings in the Midwestern U.S. since this was a single site pilot study. Because the work and study subscale was removed from our PCA and alpha Cronbach's analysis, it is inappropriate to compare our findings against those of other researchers using the DLQI.

Conclusions

Breast radiodermatitis has a profound impact on quality of life. Additional larger studies are needed using more diverse populations. In particular, the impact of breast

radiodermatitis on work and study needs further exploration. Since the variance in the work and studying subscale was zero, we are curious to learn whether this phenomenon is common among breast cancer patients receiving radiotherapy. Also, seasonal effects must be considered for longitudinal studies or when study accrual extends across seasons in skin-related quality of life research.

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Table 5.1.

Agreement between Participant Scored Ratings on the DLQI and Narratives of the Radiation Skin Changes Form

	(*n* = 31) %*
Agreement	
Symptoms & Feelings Subscale	
1. Over the last week, how itchy, sore, painful or stinging has your skin been?	71
2. Over the last week, how embarrassed or self conscious have you been because of your skin?	87
Daily Activities Subscale	
3. Over the last week, how much has your skin interfered with you going shopping of looking after your home or garden?	74
4. Over the last week, how much has your skin influenced the clothes you wear?	90
Leisure Time Subscale	
5. Over the last week, how much has your skin affected any social or leisure activities?	87
6. Over the last week, how much has your skin made it difficult for you to do any sport?	98
Work & School Subscale	
7. Over the last week, has your skin prevented you from working or studying?	97
Personal Relationships Subscale	
8. Over the last week, how much has your skin created problems with your partner or any of your close friends or relatives?	74
9. Over the last week, how much has your skin caused any sexual difficulties?	97
Treatment Subscale	
10. Over the last week, how much of a problem has the treatment for your skin been, for example by making your home messy, or by taking up time?	74

*Percentage is rounded to the nearest whole number

Table 5.2.

Measures of Reliability and Validity for the Dermatology Life Quality Index (DLQI) Subscales in Breast Radiodermatitis

	(n = 40)		Loadings	
	Correlation with other subscale items	**Alpha if subscale is removed**	**Component 1**	**Component 2**
Symptoms & Feelings Subscale	.62	.81		.82
Daily Activities Subscale	.67	.80	.73	
Leisure Time Subscale	.75	.77	.97	
Work & School Subscale	Had zero variance and was removed from the scale during principal component analysis in SPSS		NA	NA
Personal Relationships Subscale	.69	.80	.97	
Treatment Subscale	.50	.84		.96

CHAPTER 6

SKIN-RELATED QUALITY OF LIFE AMONG MIDWESTERN US COMMUNITY-BASED WOMEN WITH BREAST CANCER EXPERIENCING RADIODERMATITIS

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Abstract

Background

Little is known about skin-related quality of life among women receiving external radiotherapy for breast cancer and who experience radiodermatitis.

Objective

The aim of this pilot study was to describe the thoughts and experiences of women experiencing radiation dermatitis of the breast at a cancer program in a community setting.

Interventions/Methods

A printed survey was used to solicit feedback on the Dermatology Life Quality Index (DLQI) during the fifth week of external radiotherapy. An open-ended question inquired which DLQI-related issue was most important and why. A content analysis was conducted on the narrative responses.

Results

Twenty-eight women provided a response to the "most important" question. Sixty narratives led to the identification of 35 codes and six themes during content analysis. Themes included perspectives on having radiodermatitis, sensations caused by radiodermatitis, knowledge and preparation for radiotherapy, prevention of radiodermatitis, emotions induced by skin changes, and physical appearance of the breast skin.

Conclusions

The results of this study provide a glimpse into the perceptions of skin-related quality of life in breast cancer patients who received external radiotherapy in a community setting and experienced radiation dermatitis. Some women expressed that radiodermatitis had profound impact on their quality of life while other were surprised that radiation therapy was easy compared to chemotherapy.

Implications for Practice

Our findings parallel those found in a previous study conducted in an urban setting. The results provide insight into the thoughts and needs of women undergoing external radiotherapy of the breast. Assessing individual differences in skin-related QOL can provide can provide needed information for tailoring care to the unique needs of each woman. Additional studies focusing specifically on skin-related quality of life are needed.

Introduction

"I hope she does better than I did. I got all burnt up!" commented the daughter of a woman with breast cancer who was about to start radiation therapy. The daughter was also a breast cancer survivor. Her haunting comment inspired our study.

Radiation dermatitis is a treatment-induced dose-limiting toxicity.[1] The National Cancer Institute defines radiation dermatitis as "a skin condition that is a common side effect of radiation therapy. The affected skin becomes painful, red, itchy, and blistered."[2] Radiodermatitis can lead to treatment delay or early termination, lost work productivity, wound care costs, social isolation, and altered body image.[3,4] Thus radiodermatitis can

greatly impact quality of life.[3,4]

Three previous studies strongly informed our investigation. While many interventional studies designed to explore the efficacy of products created to prevent or manage radiodermatitis also examine skin-related quality of life as a secondary outcome, to date, only one pilot and one larger study were found that focus exclusively on skin-related quality of life in breast cancer patients receiving radiotherapy. Schnur et al.[4] conducted a pivotal qualitative study using a semistructured guide to conduct in-depth interviews of women with breast radiodermatitis at an urban major medical center that focused on women's experiences of skin changes during radiation therapy and how those skin changes impacted the women's lives. In an earlier study, Schnur et al.[5] had 15 women keep a diary of their experiences during breast radiation therapy in a pilot study. The findings of both studies will be compared with and contrasted against our results.

A study by McMullen et al.[6] also influenced the design of our pilot investigation. These researchers conducted a mailed survey study on challenges encountered by survivors of colorectal cancer with a stoma for at least five years. They included an opened-ended question at the end of the survey that asked the participant to share the greatest challenge encountered related to having an ostomy and used a qualitative approach to analyze responses to the greatest challenge question.

Most cancer research studies are conducted at major medical centers in urban locations. These settings have access to large populations that when sampled supply enough power to answer important research questions. However, only 15% of cancer patients receive cancer treatment at urban major medical centers; the remaining cancer patients receive care in community settings.[7] Therefore, it is important to conduct

research and explore the perspectives of women with breast cancer in these community settings. Environmental factors such as proximity to the cancer program and access to transportation may differentially influence the perspectives of urban-dwelling versus community-dwelling breast cancer patients. Our primary aim was to describe the thoughts and experiences of women experiencing radiation dermatitis of the breast at a cancer program in a community setting.

Design and Methods

A qualitative analysis of study participants' written responses to an open-ended survey question is presented in this article. This analysis is part of a larger, longitudinal, mixed-methods pilot study on the skin-related and global quality of life among women experiencing acute radiodermatitis of the breast in a community setting. For one portion of this pilot study, we used a survey to seek feedback from participants regarding the impact and adequacy of each item on the Dermatology Life Quality Index (DLQI) at five weeks on external radiotherapy. All aspects of the study were designed to cause minimal intrusiveness and burden for the participants who were actively receiving radiation therapy. Similar to McMullen et al.,[6] we included an open-ended question at the end of the survey. This article presents the results of a content analysis on the responses to that question.

Human Subjects Protection

The study was approved by the University of Utah Institutional Review Board (UIRB). A reliance agreement was created between the UIRB and the health care system affiliated with the cancer program. Only a unique participant identification number was

used on each study form to identify the participant to enhance maintenance of confidentiality.

Participants and Setting

A purposive sample was recruited from a Comprehensive Community Cancer Program located in a United States Census Bureau designated "urban cluster" from May 2014 to April 2015. An urban cluster is an area with a population of more than 2 500 and less than 49 999 individuals.[8] The catchment area for this cancer program is northern Illinois and southern Wisconsin including a vast rural area. Eligible participants included English-speaking females aged 18 years or older with stage 0-III breast carcinoma that had not started, but were recommended to receive external radiotherapy of the whole breast. Additional details about the sample are provided in Table 6.1. A radiation oncologist identified each woman as a candidate for external radiotherapy of the breast. The first author invited each potential participant to join the study and collected informed consent from each woman who accepted the invitation. Forty women participated in the main study and were asked to complete an open-ended survey about items on the Dermatology Life Quality Index instrument.[9] The last question on the survey inquired, "Which issue is most important and why?" Of the 40 main study participants, 28 provided a response to this question.

Procedure

The survey was provided in hard copy at the fifth week on radiation therapy when radiodermatitis was likely to begin to peak. The participant was asked to complete the survey and return it within one week. The handwritten responses were transcribed

verbatim into a single digital text file by the first author. The digital file was stored on a secure, password protected, encrypted external drive. The hard drive was locked in a fireproof safe located in a locked office when not in use.

Analysis

Our goal was to gain a greater understanding of patient-reported skin-related quality of life in the presence of breast radiodermatitis. A qualitative content analysis approach was implemented. This research method uses a flexible yet systematic classification process of coding and identifying themes to permit the subjective interpretation of the content of data.[10] This systematic approach helps to ensure the reliability and replicability of the results.[11]

Each member of the investigative team independently reviewed all of the comments. A list of initial codes was generated during telephone conferences and via email conversations. The first and second author independently assigned codes to the data. The responses were divided to represent one unique concept. None of these concepts were assigned more than one code. The third author reviewed the coded data and provided input. The results were discussed and consensus was reached. The first author reviewed the coded data to identify final codes and overarching themes. Since the participant was completing a survey about the 10 items on the DLQI, the six conceptual domains of this instrument (i.e., symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment) influenced participant's responses and informed some of the themes identified.

Results

Six themes were identified during data analysis: perspectives on having radiodermatitis, sensations caused by radiodermatitis, knowledge and preparation for radiotherapy, prevention of radiodermatitis, emotions induced by skin changes, and physical appearance of the breast skin. Numerical counts and percentages of codes were calculated to help elucidate the frequency of these concerns among the participants and are provided in Table 6.2.

Perspectives on Having Radiodermatitis

The participants described their perspectives regarding the experience of having radiodermatitis of the breast along a dynamic and vast continuum. Some women expressed a positive attitude regarding cancer care.

> -I feel very lucky and fortunate that my cancer was found early and has not spread yet. Also, I know there are many women who are not as fortunate in their diagnosis and those whom have much worse reactions to radiation.
>
> -The treatment is a little uncomfortable but if it is increasing my chances of not having a recurrence of cancer, it been just a small price to pay.

Cancer care often encroached on pre-existing plans for summer vacations, travel, school, work, and family reunions. A number of women expressed having a deadline in mind when all aspects cancer care would be completed.

> -I don't want to delay my "exchange" with the plastic surgeon. I didn't expect to have radiation at all so I'm months behind my schedule to get on with my life.

Similarly, some women in the study by Schnur et al.[4] felt there was a time when side

effects were expected to appear and to resolve. One lady commented, "This is taking too long to recover. . . I'm not going to do any more [radiation]" (p. 671).[4] Another woman wondered whether her breast would stay red and sore forever.[4]

Sensations Caused by Radiodermatitis

Thirty-two percent of the participants wrote about the physical sensations that accompany radiodermatitis of the breast. Itching, pain, and tenderness were the most commonly reported sensations.

> -For me, the extreme itchiness has been the most important issue. I have been concerned and sometimes upset, because I have been unable to get consistent relief. Although I have continued with my regular activities and what I want to do, the itchiness was always 'there'—difficult to completely ignore or forget. And, although I realize my skin did not get this way overnight and will take time to heal, I have been concerned at how long that will actually be.
>
> - The soreness and redness hurts and keeps me from doing some things that I usually do. Not a big problem but it's a constant reminder of what is and has happened to me.
>
> - The only issue of importance to me is my comfort level with the clothes I wear. This is nothing really new—wool has always itched, cashmere, silk, and fabric that does not breathe causes claustrophobia; polyester makes me sweat—'yes, cotton is the fabric of my life' says the advertising.
>
> -I feel like a grease monkey!
>
> -It feels like I am boiling inside of my breast.
>
> -My skin does not bother me as much as the expanders do!

Emotions Induced by Skin Changes

Some women in our study were open about expressing their emotions about radiation dermatitis while others hid their emotions and needs, embracing stoicism.

- How it looks like depresses me.

- I keep it in. No one knows the pain I have unless I am asked about it—and then I say 'I'm ok.'

In the study in 2009 by Schnur et al.,[5] one woman wrote her diary that since she could see the radiation skin changes, she knew "they're aiming right" (p. 672). Other women verbalized perceptions that since radiation therapy is invisible, they wondered if the treatment was being administered correctly or whether it would work.[5] A participant in the present study expressed a related concern.

-I am also concerned of what the radiation does to me. I know it's to kill the cancer but it's scary how it destroys the good tissues too. I am looking forward to the treatments being over and my body healing itself back to normal.

Many women in our study eagerly anticipated finishing radiation therapy. For most women, completion of radiation therapy heralds the end of nearly a year of cancer therapy.

-I am anxious to have the side effects of radiation behind me so I am faithful in caring for my skin.

In addition to emotions directly related to skin toxicity, it is important to consider the impact of issues occurring in the patient's life outside of the cancer experience. Two participants were widowed while receiving chemotherapy a few months before radiation therapy commenced.

- I have bigger things to worry about! I lost my husband not long ago!

One recently divorced woman needed to hold two job positions during breast cancer care. Many women needed to schedule their radiation therapy appointment at 7-7:30 am (i.e., before the cancer center officially opened) to avoid tardiness and potentially losing their daytime employment. One woman worried about her husband who was affected by Alzheimer disease wandering away while she was in the radiation treatment vault. Another was reluctant to receive radiotherapy because she needed to babysit her grandchildren so that her daughter, a single mother, could work.

Physical Appearance of the Breast Skin

Only five women expressed concerns about the physical appearance of their breast or skin. This was a very important issue for some women. For example, a participant wondered if her affected breast would ever look normal again. She previously had a breast reduction surgery years prior to her breast cancer diagnosis to improve the look of her breasts. Conversely, another woman was surprised to complete radiation with minimal skin toxicity and bother.

-You should ask how the coloring of your skin is. How that affects you . . . You don't ask if it is cracking, dry, bleeding—how the skin is. Are the creams helping?

-I have not experienced most of the effects I was expecting. I have what amounts to a mild sunburn so far.

A woman in the study by Schnur et al.[4] in 2011 commented that dermatitis was worse than a sunburn because sunburn goes away but dermatitis "just keeps getting worse" (p. 263). Lighter skinned women talked about their skin getting red, for example, "you

couldn't even find the nipple on my breast" (p. 263).[4] Darker skinned women commented about their skin getting darker, for example, "dark and ugly, too dark, like toast when it burns, black and crispy, burnt, and charcoal" (p. 263).[4] Participants in our study and in the study by Schnur et al.[4] commented about radiodermatitis causing a greater need to cover up during the summer.

Prevention and Management of Radiodermatitis

Nine of the 40 participants mentioned an aspect of preventing or managing radiation dermatitis. There were vigilant about inspecting skin in the radiation treatment field and applying prescribed creams.

> -The most important issue is keeping my skin healthy and moisturized while in treatment.
>
> - Making sure that my skin improves a little bit each day so that I don't have any open sores or infection.

A number of women commented about adjusting clothing selection or physically altering clothing to enhance comfort, keep prescribed creams in place and without ruining clothing, and to avoid worsening of moist desquamation caused by clothing friction.

> - I think just the right choice of clothes to wear and can make a difference of comfort throughout the day.
>
> - I am wearing my husband's old tee shirts. I do not want to ruin good clothes!
>
> - I am going to Goodwill today. I am going to buy some old tee shirts. I am going to cut the arms off and leave a big hole so that it does not rub the sores under my arm.

-One woman commented about applying cream to the radiation site and wearing her bra over the camisole to keep the cream in place while she worked.

Comparably, women in the study by Schnur et al.[4] in 2011 commented about having to go braless, changing from an underwire bra to one without an underwire, wearing a camisole or undershirt; or needing to wear loose clothing, only black bras, or old t-shirts because of greasy, oily skin creams.[4] Large breasted women discussed inability to go to church and family functions such as weddings because they were unable to wear an underwire bra.[4]

Knowledge and Preparation for Radiotherapy

Although each patient is taught by a radiation oncology nurse and radiation therapist, some women that experienced the most severe skin toxicity believed radiation skin changes were downplayed by the healthcare team. These women thought every breast cancer patient that receives radiotherapy develops severe skin toxicity and they recommended additional teaching before the start of radiation therapy.

- There seems to be more concern with how the skin 'looks' rather than how it 'feels' to the individual. Radiation skin changes probably follow a pattern on a continuum. I would have liked to have had a visual aid and descriptive of some sort to show that.

-I feel an important issue is how you are going to feel. The more you know the better. Everyone is different and reacts different but if you have a really good idea how your skins going to feel you can be prepared on how to dress and your social life.

Similarly, in the report of their pilot study, Schnur et al.[5] recommended increased patient

education about what to expect during radiotherapy.

Discussion

The study was an attempt to describe the thoughts and experiences of women at a cancer program in a community setting who were experiencing breast radiodermatitis and to extend our understanding of quality of life in this population by exploring the rich information provided by these women. Twenty-eight participants provided 60 narratives from which 36 codes were identified. The codes led to the generation of six themes including perspectives on having radiodermatitis, sensations caused by radiodermatitis, emotions induced by skin changes, physical appearance of the breast skin, prevention and management of radiodermatitis, and knowledge and preparation for radiotherapy. The themes suggest that radiodermatitis has a significant impact on quality of life.

Some of our results closely mirror those of Schnur et al.[4-5] The dimensions of QOL identified by Schnur et al.[4] (e.g., physical discomfort, body image disturbance, emotional distress, and impairment of day-to-day functioning) are similar to the DLQI subscales (i.e., symptoms & feelings, daily activities, leisure, work & school, personal relationship, treatment). We asked participants which DLQI item was most important and why. Most of the themes identified in our study relate to DLQI items and subscales.

The participants in our study wrote about concerns not voiced by the participants in the study by Schnur et al.[4] For example, our study participants mentioned the sensation of boiling inside, the importance of selecting fabric that breathes, and concerns about future recurrence. To the authors' knowledge, this is the first study to mention a sensation of boiling inside the breast among breast cancer patients and a preference for clothing fabric that breathes. Participants in previous studied reported a burning sensation or

appearance of the skin.[4,12] Similarly, a preference for soft and loose clothing was reported in a previous study,[4] but did not include natural fabric such as cotton that breathes. While not reported by Schnur et al.,[4] fear of breast cancer recurrence has been reported in other studies[13] and therefore is an important consideration when studying quality of life in this population.

Strengths and Limitations

This study portrays the perceptions and experiences of women receiving breast cancer care in a community setting. To the authors' knowledge, this is the first study with a primary outcome focusing on skin-related quality of life among women experiencing breast radiodermatitis in a community setting. It was important to compare our findings in a community setting against those of Schnur et al.[4] in an urban setting to determine the generalizability of both sets of findings. There were many similarities and a few differences in these findings. Although our sample represents one community which has limited diversity, it may characterize much of the Midwestern U.S. and provide a foundation for future studies.

We conducted a small pilot study to inform larger future studies. Therefore, the sample size was modest. Our participants provided insightful responses to the most important issue question, but they did so independently which did not allow for professionally probes. We can use this information to design a future study that will allow for probes.

Conclusions

The results of this study provide an important glimpse into the perceptions of breast cancer patients who received external radiotherapy in a community setting and experienced radiation dermatitis. Each person has a unique view of personal health. Our results show a broad range of responses. Several women expressed that radiodermatitis had profound impact on their quality of life while others were surprised that radiation therapy was easily tolerated as compared to chemotherapy. Two important new findings were identified: a boiling sensation within the breast not on the skin surface and a preference for clothing fabric such as cotton that breathes.

Future Directions

Additional studies in community settings across the U.S. are needed to compare against our results, including additional cultural and ethnic groups. More studies are required to describe of breast radiodermatitis among women with inflammatory breast cancer, men, and transgender women.

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Table 6.1 Sample Characteristics (n = 28)

Characteristic	Range	Mean	SD
Age in Years	40-82	59.43	11.9
		n	**%**
Race/Ethnicity			
Non-Hispanic White		27	96.4
Asian/Pacific Islander		1	3.6
Level of Education			
Less than high school graduation		1	3.6
High school graduate or GED		5	17.9
Vocational training after high school		1	7.1
Some college or associate degree		11	39.3
College graduate (B.A. or B.S.)		8	28.6
Master's degree		1	3.6
Occupation			
Homemaker or housewife		3	10.7
Professional specialty or manager		9	32.1
Technical, retail, administrative support, or skilled worker		9	32.1
Service		2	7.1
Laborer		2	7.1
Other		3	10.7
Annual Income (range)			
Under $15,000		3	10.7
$15,001-$25,000		1	3.6
$25,001-$35,000		2	7.1
$35,001-$45,000		1	3.6
$45,001-$60,000		4	14.3
$60,001-$75,000		5	17.9
Over $75,000		12	42.9
Cancer Stage			
0 (Tis)		4	14.3
I		5	17.9
IIa		10	35.7
IIb		1	3.6
IIIa		4	14.3
IIIb		2	7.1
IIIc		2	7.1
Histology			
Ductal		19	67.9
Lobular		5	17.9
DCIS		4	14.3
Grade			
1		3	10.7
2		13	46.4
3		12	42.9
Surgery			
Did not have surgery		1	3.6
Lumpectomy		18	34.2
Mastectomy with immediate reconstruction		4	14.3
Mastectomy without reconstruction		5	17.9
Chemotherapy before Radiotherapy			
Yes		17	60.7

Abbreviation: SD, standard deviation

Table 6.2 Descriptive Data for Codes and Themes (Total Narratives = 60; Total Codes = 36)

Themes	n (%)	Codes	n
Perspectives on Having Radiodermatitis	13 (22)	Could be worse	2
		Stay positive	2
		Social activities and family are important	1
		Very lucky and fortunate	1
		Happy only had 3 weeks of (dose dense) treatment	1
		Want to move on	1
		A purpose	1
		Difficult to maintain 100% positive	1
		Skin is a constant reminder of cancer experience	1
		Blocking time for radiation therapy	1
		Months behind on my schedule	1
Sensations Caused by Radiodermatitis	19 (32)	Itching	7
		Tenderness	7
		Boiling inside of my breast	1
		Comfort level is important	1
		Fabric that does not breathe causes claustrophobia	1
		I feel like a grease monkey	1
		Breast expanders cause bother	1
Emotions Induced by Skin Changes	8 (13)	Depression about breast appearance	2
		Stoicism (hiding emotions)	1
		Fear of radiation therapy	1
		Concern for future recurrence	1
		Eager to recover	1
		Have bigger things to worry about	1
		Pleasantly surprised	1
Physical Appearance of the Breast Skin	5 (8)	Coloring of skin	1
		Cracking	1
		Dry	1
		Bleeding	1
		[Like a] mild sunburn	1
Prevention and Management of Radiodermatitis	9(15)	Choosing or creating the right clothes	4
		Faithful in caring for my skin	2
		Keeping skin healthy and moisturized	2
		Trying to avoid blisters and tearing	1
Knowledge and Preparation for Radiotherapy	6 (10)	Knowing what to expect	5
		Visual and descriptive to show radiation skin changes	1

CHAPTER 7

A PILOT STUDY OF THE IMPACT OF BREAST BREAST RADIODERMATITIS ON SKIN-RELATED AND GLOBAL QUALITY OF LIFE

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Abstract

Purpose

To explore the relationship between skin-related and global quality of life among women experiencing breast radiodermatitis; describe the change in and determine factors related to skin-specific and global quality of life (QOL) among women undergoing external radiation therapy for breast cancer at week five on radiotherapy.

Methods

Forty women undergoing whole breast 3-dimensional conformal radiotherapy at a community cancer center completed the Dermatology Life Quality Index (DLQI) and Quality of Life-Breast Cancer Patient Version at baseline before and at five weeks on radiotherapy. Skin toxicity was measured using the Radiation Therapy Oncology Group (RTOG) Acute Radiation Morbidity Scoring Criteria-Skin scale. A Kendall's tau correlation was used to explore the relationship between measures of skin-related and global QOL

Results

In general, skin-related and global quality of life was highly correlated. Skin-related QOL changed profoundly ($p<.001$) while global QOL did not change ($p=.55$) between baseline and five weeks on radiotherapy.

Conclusions

Radiation-induced skin toxicity has a major impact on many subtypes of skin-related but not as strongly on global QOL. Additional larger studies in more diverse populations are needed.

Background

Skin toxicity is a common issue among women receiving radiotherapy for breast cancer. The incidence of radiodermatitis of the breast ranges up to 100%.[1] Few studies have examined the impact of breast radiodermatitis on quality of life as a primary outcome. Schnur et al.[2] found in their 2009 pilot study that breast cancer patients receiving radiotherapy perceived there is a time when symptoms should appear and a time when those symptoms should resolve; the patients feared cancer recurrence, receiving the wrong treatment, or the symptoms may never end; the patients perceived themselves as physically repulsive and felt guilty about not being able to do everything they did before the breast cancer diagnosis. In 2011, these researchers followed the pilot with a larger study. In this second study, breast cancer patients commented that sunburns go away, but radiation burns keep getting worse; they were anxious for their skin's appearance to return to normal; they often needed adapt their clothing and this impacted their social activities.[3] Wadasadawala et al.[4] found similar results in women who received whole breast radiotherapy had worsened perception of body image and more financial concerns than women who received interstitial multicatheter brachytherapy.

Knobf and Sun[1] found women undergoing radiotherapy for breast cancer reported experiencing pain, twinges, skin changes, fatigue, sleep disturbances, and breast edema. Comparably, women in the study by Wengström et al.[5] described having pain, skin changes, and fatigue at the end of breast radiotherapy. All of the participants in Knobf and Sun's[1] study experienced a skin change by the fifth week of radiotherapy. Similarly, 100% of the breast cancer patients in a study by Berthelet et al.[6] developed skin toxicity during external radiotherapy. The results of these studies demonstrate that women

receiving external radiotherapy for breast cancer are likely to develop radiodermatitis and experience a detrimental effect on their QOL.

A number of studies focused on testing agents to prevent or manage skin toxicity and measure quality of life (QOL) as a secondary outcome. For example, Rollmann et al.[7] investigated the efficacy of emu oil as compared to cottonseed oil to reduce skin toxicity and maintain higher levels of skin-related and global QOL. Chan et al.[8] also used skin-related QOL as a secondary outcome when comparing the use of allantoin versus aqueous cream to reduce skin reactions. Hindley[9] investigated the value of mometasone furoate and diprobase creams to reduce radiation skin reaction of the breast. Participants in the mometasone furoate arm enjoyed better skin-related QOL.

Receiving chemotherapy prior to radiotherapy has a negative impact on QOL among breast cancer patients. The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-30 (EORTC-QLQ-30) is a well-validated instrument composed of scaled items.[10] The potential total transformed score for the EORTC-QLQ-30 ranges from zero to 100, with higher scores representing better QOL.[11] Marino et al.[12] measured QOL on the first day of the last cycle of chemotherapy and at the end of radiotherapy among women with breast cancer. The median score for global QOL in the general population is 75 and role functioning is over 83.3.[10] The mean score for global QOL was 60.19 in the standard chemotherapy and 59.13 in the high dose chemotherapy group on the first day of the last chemotherapy cycle.[12] Further, the mean score for role functioning was 60.62 in the standard and 35.61 in the high dose chemotherapy group at the end of radiotherapy.[12]

In summary, radiodermatitis is a common toxicity in breast radiotherapy. It

impacts body image, clothing selection, and ability to engage in activities of daily living. Skin-related and global QOL are often used as secondary outcomes in studies designed to test the efficacy of agents to prevent or manage radiodermatitis in previous studies. Additional studies that explore skin-related and global QOL in the presence of radiodermatitis are needed. We sought to help fill that knowledge gap.

Methods

Study Aims

The aim of this pilot study was to investigate the impact of breast radiodermatitis on skin-related and global quality of life. More specifically, we sought to:

1. Explore the relationship between skin-related and global quality of life among women experiencing breast radiodermatitis.
2. Measure change in skin-related and global quality of life before the start of and at week five on radiation therapy when radiodermatitis was expected to begin to reach peak level.

Design

A longitudinal study using repeated measurements was implemented to explore the study aims.

Sample and Setting

A purposive sample of 40 women undergoing 3-dimensional conformal radiotherapy for breast cancer was recruited. The study was conducted in a single radiation department in a community setting in northern Illinois.

Ethical Approval

Ethical approval was gained from the University of Utah Institution Review Board (UIRB), Salt Lake City, Utah, USA. A reliance agreement was created between the UIRB and the health care system affiliated with the cancer program. All participants gave informed consent before inclusion in the study.

Study Measures

RTOG Acute Radiation Morbidity Scoring Criteria-Skin (RTOG score)

The Radiation Therapy Oncology Group (RTOG) score is measured using an ordinal scale with a range of 0 to 4. The number represents level of skin toxicity. Zero corresponds to "no change from baseline" and level 4 corresponds to "ulceration, hemorrhage, necrosis."[13] The RTOG score is used to identify the maximum level of skin toxicity in the entire radiation treatment field. It was developed by radiation oncology experts in 1985 to complement the existing criteria for late-onset skin toxicity, but has not been formally validated.[14]

Breast Skin Assessment Form (BSAF)

The BSAF is an investigator-developed tool designed to collect the RTOG skin toxicity score for seven areas in the breast radiation treatment field, maximum score, sum of the seven scores, cumulative radiation dose, a line drawing of a breast image, identification of laterality of breast treated, and comment section. These data were collected by the PI at baseline, then weekly during radiation therapy.

Dermatology Life Quality Index (DLQI)

The DLQI is a 10-question instrument that explores the participant's perception of skin condition impact on quality of life. It was designed to minimize survey burden when used weekly. Weighted scores range from 0 to 30 with higher scores indicating worsening quality of life.[16] The independently investigated and reported reliability of the DLQI for use among individuals with psoriasis and eczema was a Cronbach's alpha of .83.[16] The DLQI was previously used for but formally validated for use in radiodermatitis. This instrument was completed by participants in the current study at baseline and weekly during radiotherapy.

Quality of Life-Breast Cancer Patient Version (COH-QOL-Breast)

The City of Hope Quality of Life-Breast Cancer Patient Version is an instrument consisting of 46 ordinal scale items that measure the participant's perception of breast cancer impact on global health-related quality of life.[17] The total score can range from 0 to 460. Traditional coding of responses on the COH-QOL-Breast leads to a higher score indicating better quality of life. The reported overall Cronbach's alpha for the COH-QOL is r =.89 and is r = .81 for the social concerns, r = .88 for the physical well-being, r = .88 for the psychological well-being, and r = .90 for the spiritual well-being subscales.[18] A comparison of the DLQI and COH-QOL-Breast instruments is provided in Table 7.1.

Analytic Strategy

A Kendall's tau correlation was used to explore the relationship between measures of skin-related and global QOL. Responses on the COH-QOL-Breast were recoded so that a higher score indicated worsened QOL to enhance interpretation of this

correlation. Paired *t*-tests were used to measure the change in skin-related and global QOL from baseline to the fifth week on radiotherapy.

Results

Sample

The 40 adult female participants of this pilot study were undergoing external radiation therapy. They were primarily White, middle-aged, nearly obese, previous smokers, and likely to experience a sunburn. Eligibility criteria included stage 0-III breast cancer but most had had stage IIa or less, grade 2, estrogen and progesterone receptor positive, ductal carcinoma treated by lumpectomy and chemotherapy. None of the women received concurrent hormone therapy. Additional details are reported in Table 4.1 (i.e., Chapter 4) of this dissertation.

Relationship Between Skin-related and Global QOL

The DLQI and COH-QOL-Breast were coded so that higher scores indicated worsening QOL. All 40 participants responded on the DLQI at five weeks on radiotherapy that their skin did not interfere with work or study. Since all participants reported their skin did not interfere with work or study, this item could not be correlated with other measures. All other components of the DLQI were highly intercorrelated. The spiritual well-being subscale of the COH-QOL-Breast was not significantly correlated with any component of the DLQI or COH-QOL-Breast instruments. Conversely, psychological well-being, the composite score for the COH-QOL-Breast subscales, skin-related symptoms and feelings, and composite score for the DLQI were significantly correlated with all of the remaining measures of QOL. As overall skin-related QOL as

measured by the DLQI, skin-related symptoms and feelings, psychological well-being, and overall global QOL worsened, all other measurements of QOL significantly declined at week five on radiotherapy. See Table 7.2 for additional information.

Changes in Skin-related and Global QOL During Radiotherapy

Paired *t*-tests were used to measure the difference in skin-related and global QOL between baseline and five weeks on radiotherapy. All aspects of skin-related QOL, except for attending work and school, significantly worsened between the baseline before the start of and five weeks on radiotherapy. Using the mathematical standards for interpreting effect size set by Cohen,[19] the negative effect on skin-related QOL was small, ranging from .06 to .22. See Table 7.3 for additional information. However, using the clinical standards set by Basra et al.[20] and the DLQI raw scores measured at the fifth week on radiotherapy, 30% of the women experienced no effect (raw score 0-1), 40% experienced a small effect (2-5), 25% experienced a moderate effect (6-10), 5% experienced a very large effect (11-20), and none experienced an extremely large effect (21-30). Interestingly, global QOL did not significantly change between baseline and five weeks on radiotherapy, suggesting global QOL is more stable than skin-related QOL during radiotherapy. Also, a greater amount of impact on QOL is required to cause a significant change in a 46-item instrument as compared to one with only 10 items. Physical and psychological well-being worsened slightly, while social concerns, spiritual well-being, and overall global QOL improved minimally between baseline and week five on radiotherapy. See Table 7.4 for more details.

Discussion

We aimed to describe the impact of breast radiodermatitis on skin-related and global quality of life. Skin toxicity did not prevent those participants who were employed from working at week five on radiotherapy. This was evident by zero variance during statistical analysis for the DLQI work and study subscale among all participants.

The indicators of spiritual well-being were not significantly related to other aspects of skin-related and global QOL in this study. While we do not know the exact reason for these null results, they may relate to the fact that spirituality is a subjective experience: more important to some participants and less important to others.[21] Conversely, other factors such as physical discomfort may represent symptoms that cancer patients experience somewhat in common.

Worsening overall skin-related QOL and the skin symptoms and feelings subscale was significantly associated with a decline in global QOL, physical and psychological well-being, and social concerns. Similarly, declining psychological well-being was strongly associated with worsened overall skin-related QOL, symptoms and feelings, daily and leisure activities, personal relationships, and treatment. However, there was only a negligible change in global QOL between baseline and week five on radiotherapy. This suggests that some aspects of skin-related QOL such as symptoms (i.e., pain, itching burning) have a profound impact on global QOL; while other components of skin-related QOL have less impact on global QOL.

All measures of skin-related QOL significantly worsened between baseline and the fifth week of radiotherapy. To our knowledge, this is the first study prospectively measuring skin-related QOL as a primary outcome during breast radiotherapy. Most

studies on breast cancer-related quality of life as a primary outcome have focused on cancer survivors who have completed treatment, not those actively receiving radiotherapy.[2,3] A number of studies use QOL as a secondary outcome when comparing 2 interventions to manage radiodermatitis. However, it is important to study QOL as a primary outcome among patients actively receiving treatment because QOL data can be used to predict the onset of cancer treatment-related toxicities.[24,25] Additionally, QOL data can be used as an endpoint in cancer clinical trials and to guide clinical care as does laboratory data.[24,25]

We measured the maximum grade of skin toxicity in 7 areas of the breast treatment field weekly during radiotherapy and summed these scores each week. The clinical significance of these summed scores remains to be determined. However, the individual toxicity score for site in the treatment field combined with skin-related QOL might be useful for testing the efficacy of a radiodermatitis prevention or management intervention for that specific treatment site. For example, an agent may work well on the surface of a breast quadrant but not in the inframammary fold or vice versa.

Our pilot study had some limitations. The sample size was modest, included primarily non-Hispanic White women, and included a single site in the Midwest.

Conclusions

Other investigations support the results of our pilot study that breast radiodermatitis has a profoundly negative impact on QOL. More specifically, our results indicated all aspects of skin-related QOL, except for work and school, significantly worsened between the baseline and five weeks on radiotherapy. On the other hand, global

QOL did not significantly change between baseline and five weeks on radiotherapy. Additional larger studies among more diverse populations are required.

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Table 7.1.

Characteristics of the Dermatology Life Quality Index (DLQI) and City of Hope Quality of Life-Breast Cancer Patient (COH QOL-Breast) Instruments

	DLQI	COH QOL-Breast
Number of items	10	46
Response scale	Ordinal, narrative options	Ordinal, numeric scale options
Recall period	Over the last week	Previous experience
Subscales/Domains	Symptoms and feelings (2 items) Daily activities (2 items) Leisure (2 items) Work and school (1 item with 2 parts) Personal relationships (2 items) Treatment (1 item)	Physical well-being (8 items) Psychological well-being (23 items) Social concerns (9 items) Spiritual well-being (7 items)
Comment	One item has two parts. The first part is answered yes, no, or not relevant. Participants who answer "no" are asked to respond to the second part of the item which has a scaled response.	

Table 7.2.

Intercorrelations among Skin-related and Global Measures of Quality of Life in Women with Breast Cancer at Week 5 on Radiotherapy (n = 40)

		Skin-related QOL						Global QOL				
		1	2	3	4	5	6	7	8	9	10	11
Skin-related QOL	1. DLQI Composite	------										
	2. Symptoms & Feelings	.724**	------									
	3. Daily Activities	.695**	.414**	------								
	4. Leisure Time	.638**	.510**	.557**	------							
	5. Personal Relationships	.547**	.384**	.457**	.815**	------						
	6. Treatment	.660**	.525**	.452**	.348*	.350*	------					
Global QOL	7. COH-QOL Composite	.362**	.248*	.266*	.321*	.307*	.314*	------				
	8. Physical Well-Being	.250*	.303*	.125	.227	.204	.195	.599**	------			
	9. Psychological Well-Being	381**	.269*	.308*	.394**	.355**	.333**	.804**	.501**	------		
	10. Social Concerns	.351**	.268*	.217	.295*	.349**	.323*	.597**	.395**	.510**	------	
	11. Spiritual Well-Being	-.063	-.111	.067	-.147	-.172	-.018	.189	.080	.084	.004	------

** Kendall's tau correlation is significant at the 0.01 level (2-tailed)

* Kendall's tau correlation is significant at the 0.05 level (2-tailed)

The COH-QOL-Breast scores were coded in the traditional manner so that higher scores indicate worsened QOL

Table 7.3

Change in Skin-related QOL between Baseline and 5 Weeks on Breast Radiotherapy (n = 40)

	Mean Score at Baseline	SD at Baseline	Mean Score at Week 5	SD at Week 5	*t*-statistic	P value	Mean Difference	95% CI	η^2
Symptoms & feelings	.25	.67	1.50	1.01	-7.16	< .001	-1.25	-1.60 to -0.90	-.22
Daily activities	.13	.46	.93	1.02	-4.97	< .001	-.80	-1.13 to -0.47	-.15
Leisure	.00	.00	.43	.90	-2.98	.005	-.43	-0.71 to -0.14	-.08
Work & school	.00	.00	.00	.00	--------	--------	.00	-------	-------
Personal Relationships	.03	.16	.28	,75	-2.04	.05	-.25	-0.68 to -0.00	-.06
Treatment	.00	.00	.63	.03	-4.90	< .001	-.63	-0.88 to -0.37	-.14
Total	.40	1.19	3.88	3.55	-6.32	< .001	-3.48	-4.59 to -2.36	-.19

Degrees of freedom (df) = 39 for all analyses

Table 7.4

Change in Global QOL between Baseline and 5 Weeks on Breast Radiotherapy (n = 40)

	Mean Score at Baseline	SD at Baseline	Mean Score at Week 5	SD at Week 5	*t*-statistic	P value	Mean Difference	SD for Mean Difference	95% CI
Physical well being	60.03	13.61	60.53	14.13	-.29	.78	-.50	45.59	4.03 to 3.05
Psychological well being	134.25	44.01	130.75	45.04	.73	.47	3.50	11.11	-6.22 to 13.22
Social concerns	59.35	18.32	58.28	19.41	.52	.60	1.08	30.38	-3.08 to 5.23
Spiritual well-being	43.28	13.23	43.00	13.86	.18	.86	.28	13.00	-2.88 to 3.43
Total	296.90	74.18	292.55	72.23	.60	.55	4.35	9.87	-10.23 to 18.93

Degrees of freedom (df) = 39 for all analyses
The COH-QOL-Breast scores were coded in the traditional manner so that higher scores indicate better QOL.

CHAPTER 8

SUMMARY

Introduction

In this final chapter of the dissertation, a synopsis of the study findings, description of limitations and strengths of the study design, recommendations for future research, and recommendations for clinical practice are discussed. Then, conclusions regarding the study are provided. A synopsis of the participants that took part in each portion of the study is illustrated in Figure 8.1.

Study Findings

We conducted a feasibility and pilot study of the impact of radiodermatitis on skin-related and global quality of life (QOL). Our study results may help inform other future studies. However, given the pilot nature of this study, caution must be taken regarding the application of our results to the care of breast cancer patients. The results of our feasibility and pilot study are described in greater detail in Chapter 4 of this dissertation.

Feasibility of Study Design and Measures

We carefully examined the pilot study design and measures. Field notes were taken throughout the study duration. Recruitment during the radiation oncology consultation visit worked best among participants in our setting. The retention rate was

98%. The refusal rate was 18% with the most common reason for refusal provided being I "feel really overwhelmed right now."

A few changes are recommended for future studies. We suggest including individuals with inflammatory breast cancer who have undergone mastectomy, individuals with skin conditions affecting the breast, men, and transgender women. These individuals are frequently excluded from study participation. Consequently, we do not know how radiodermatitis differs in these individuals. They can be followed closely during studies and reported as a case study if their response differs significantly from the other study participants.

We recommend some changes to our data collection forms. The maximum income range collected should be increased beyond $75,000 per year to examine the impact of higher income on perceptions and outcomes. A breast skin assessment form should be created with an image of a chest wall for use in participants who had a mastectomy without immediate reconstruction. Scannable forms would decrease the time required to enter data. The forms would still require checking for accuracy by comparing the primary source against information in the electronic database.

Collecting clinician-measured breast length took less than 1 minute and cost about $0.15 for each participant. This time requirement and financial cost was deemed feasible in our study. Moreover, each study participant agreed to have her breast length measured.

The vast geographic distance between the cancer program and PI's place of employment created a challenge to avoid missing weekly data observations and losing opportunities to invite prospective participants to join the study. Having a research nurse

onsite with approximately 50% effort dedicated to a study conducted in a community setting likely would have shortened the time required to recruit a sample size of 40 individuals. Measuring skin toxicity by preset cumulative radiation doses might have been feasible with a research nurse onsite at the cancer program.

Breast Characteristics

Participant-reported bra cup size and clinician-measured breast length were discordant in our study. For example, women reporting a C bra cup size had clinician-measured breast lengths ranging from 5.0 to 12.5 centimeters (cms). Similarly, women reporting a D bra cup size had measured breast lengths ranging from 7.5 to 10.5 cms. This finding is important because in most studies of interventions designed to prevent or manage breast radiodermatitis a D cup is categorized as a large breast and a C cup as an average-sized breast. Participant-reported bra cup size was an imprecise estimate of the actual breast size in our study.

Increase in breast length significantly correlated with increase in maximum RTOG score ($p = .04$); increased RTOG score in the upper medial breast quadrant ($p = .04$), upper lateral quadrant ($p = .02$), lower lateral quadrant ($p = .02$), inframammary fold ($p = .001$); with increasing BMI ($p = .002$) and bra cup size ($p = .0003$). Although participant-reported bra cup size and clinician-measured breast length were discordant breast length and bra cup size were significantly positively correlated ($p = .0003$).

Multiple Measurements of Skin Toxicity

Assessing skin toxicity grade in seven areas within the radiation treatment field was easy to do when recorded on our breast skin assessment form. A one-way within-subjects repeated measures ANOVA was conducted to compare skin toxicity grade of the

breast using the RTOG scoring system by each individual area in the radiation treatment field and the total of all scores at baseline then weekly during radiotherapy. The means, standard deviations, Wilk's Lambda, *F* statistic, degrees of freedom, significance level, and eta squared are presented in Table 4.5 of Chapter 4 in this dissertation. Skin toxicity significantly increased with time on radiation treatment in every site within the radiation treatment field. There was a significant effect size (η^2) for time in each area in the treatment field, ranging from $\eta^2 = .60$ to .89 with the smallest effect in the subclavicular area and the largest effect in the axilla. The effect of time on the total toxicity score for all areas was $\eta^2 = .90$, $p < .001$. Every participant experienced a grade 1 or higher skin toxicity by week 5 on radiotherapy. We recommend retaining each of the seven measurements in the radiation treatment field. Although the subclavicular area was least effected, it was a very important assessment for some participants. Also, we recommend completing the assessment weekly to allow for comparison of results against other scientific studies.

Impact of Radiodermatitis on QOL

Participants completed the Dermatology Life Quality Index (DLQI) instrument weekly while receiving external radiotherapy of the female breast. At week 5 on treatment, 31 (78%) participants provided narrative feedback on how each DLQI item impacted her life. Agreement between the DLQI numerical ratings and the narrative feedback was assessed. Agreement between DLQI ratings and narratives ranged from .71 to .98. Construct validity was estimated using principal component analysis (PCA). The DLQI work and study subscale was removed from our analyses because the variance was zero. PCA supported the inclusion of all of the remaining subscales. Reliability of the

DLQI was assessed using Cronbach's alpha. The DLQI subscales sans the work and study subscale demonstrated good internal consistency, $\alpha = .84$.

As overall skin-related QOL as measured by the DLQI, skin-related symptoms and feelings, psychological well-being, and overall global QOL as measured by the Quality of Life Instrument - Breast Cancer Patient Version (COH-QOL-Breast) worsened, nearly all other measurements of QOL significantly declined at week 5 on radiotherapy. Skin-related QOL changed profoundly ($p<.001$) while global QOL changed minimally ($p=.55$) between baseline and 5 weeks on radiotherapy. Lower income was significantly related to worsened skin-related QOL ($p=.022$); while preradiation chemotherapy predicted poorer global QOL ($p=.01$). Maximum skin toxicity predicted decreased global QOL ($p=.05$), but only showed a trend toward decreased skin-related QOL ($p=.055$).

In addition measuring agreement between participant ratings on the DLQI and their narrative feedback on how the construct of the item impacted their life, we asked an open-ended question that inquired which DLQI-related issue was most important and why. A content analysis was conducted on the narrative responses to the "most important" question. The themes identified included perspectives on having radiodermatitis, sensations caused by radiodermatitis, knowledge and preparation for radiotherapy, prevention of radiodermatitis, emotions induced by skin changes, and physical appearance of the breast skin.

Limitations

Our study was limited by a small sample size. For example, we could have estimated construct validity of the COH-QOL-breast in our study population using factor

analysis if we had 460 study participants. The diversity among the participants was limited. There was only one woman of color in the study. Men were excluded from participation, but their perceptions and risk for radiodermatitis development are important too. We focused on woman receiving external radiotherapy, not women receiving intra-operative or other partial breast irradiation modalities. Also, a single site in a Midwestern community setting was used in our study. While it is important to include cancer programs in community settings, our study design would have been stronger if it included multiple community cancer programs located in multiple geographic regions of the USA. Therefore, the results may not be generalized to the entire population of breast cancer patients in the USA.

We studied women receiving normofractionated or accelerated external radiotherapy provided in the supine position using 3-dimensional conformal techniques at a community cancer center in northwestern Illinois. Early studies investigating newer methodologies such as intensity modulated radiotherapy (IMRT) reported decreased skin toxicity as compared to older radiotherapy techniques. Studies by Freedman et al. (2009) showed a grade 3 toxicity (i.e., moist desquamation or bleeding from mild trauma; National Cancer Institute Cancer Therapy Evaluation Program, 2010) rate of 21% and Pignol et al. (2008) reported a grade 3 toxicity frequency of 31.2% in women receiving breast IMRT. However, recent studies of radiodermatitis in breast IMRT have demonstrated a higher incidence of grade 2 or greater skin toxicity. For example, De Langhe et al. (2014) reported a 58% incidence of grade 2 or higher skin toxicity among women receiving breast IMRT. Further a study by Pignol, Vu, Mitera, Bosnic, Verkooijen, and Truong (2015) demonstrated a 32.7% incidence of grade 3 skin toxicity

among women receiving breast IMRT. These results support the need for skin-related toxicity measurement no matter the method of external radiotherapy given.

Strengths

We conducted a pilot and feasibility study to inform a future larger study. Worldwide economic changes have led to reduced funding for research and we need to spend our research dollars wisely (Boadi, 2014; National Science Board, National Science Foundation, 2008). Pilot and feasibility studies must become the norm before larger studies to improve the likelihood of successful completion of larger, expensive studies. Also, pilot and feasibility studies need to be highly valued in the realm of grant reviews and academia.

Recommendations for Future Research

Greater participation in research by cancer programs in community settings is needed to improve the generalizability of cancer research findings. At least 85% of cancer patients receive treatment at community cancer programs (National Cancer Institute, 2014). Offering access to cancer and genetic research in community settings allows the participant to remain in that local setting surrounded by her or his significant others and receive continuity of health care from familiar health care providers. The National Cancer Institute Community Oncology Research Program (NCORP, 2015) provides a partial solution to this issue. However, a majority of cancer programs in community settings do not participate in NCORP. In addition, international collaboration is needed to include cancer programs in community settings in countries other than the USA. This may lead to truly generalizable cancer and genetic research results.

We found a florid distribution of radiodermatitis following the line where the inframammary fold is normally found in 1 participant who received a mastectomy without immediate reconstruction. This suggests the increased incidence and severity of radiodermatitis is not exclusively related to friction, traction, or bolus effects of an intact pendulous breast, but is potentially related to remodeling that occurs with breast development and growth. Additional observations are needed to determine whether this phenomenon occurs in other women. The hypothesis might be tested using samples of inframammary fold skin from pathology specimens submitted after breast reduction surgery.

Additional studies are needed to test the contribution of genetic and inflammatory markers to radiodermatitis. A number of candidate genes and inflammatory markers have been identified *in vitro* and in murine models of radiodermatitis development (Xiao et al., 2005). The association between some genes and inflammatory with increased development of radiodermatitis has been identified in humans. See Table 8.1 and 8.2 for additional information on selected genes and inflammatory markers with a known or suspected relationship with radiodermatitis. It is estimated that genetic disposition may play a role in the development of 80-90% of radiation dermatitis cases (Ho, 2006). Additionally, genetic predisposition to radiation dermatitis may indicate tumor sensitivity to radiation therapy (Ho, 2006).

Inflammatory markers may be related prodromal symptoms experienced by the patient, but not yet perceived by the clinician. These prodromal symptoms may influence quality of life and might therefore be indirectly assessed by measurement of skin-related QOL. This relationship must be tested in future studies. A conceptual model of that future

study including measurement of genetic and inflammatory markers possibly related to breast radiodermatitis is illustrated in Figure 8.2.

Predictors of breast radiodermatitis are the focus of a number of studies (e.g., Brown & Rzucidlo, 2011; De Langhe et al., 2014; Hymes et al., 2006; McQuestion, 2011; Salvo et al., 2010). Future research looking at predictors of QOL in women with breast cancer is needed. For example, social support may predict skin-related and global QOL in the presence of breast radiodermatitis. "Social support refers to the various types of support (i.e., assistance/help) that people receive from others" (Seeman & Psychosocial Working Group, 2008, para 1). Types of social support include emotional assistance such as empathy and reassurance, information intended to provide guidance, and instrumental support involving assistance with physical and financial needs (Cohen, 2004). This social support is provided through interactions with one's social network (Umberson & Montez, 2010). The social network includes significant relationships such as family, friends, and community (Umberson & Montez, 2010). It is important to consider social support in breast cancer because it impacts health outcomes (Umberson & Montez, 2010). Manning-Walsh (2005) found personal support was positively correlated to quality of life among breast cancer survivors and partially mediated the effects of symptom distress. In a study of 3,139 breast cancer survivors, larger social networks were associated with higher QOL (Kroenke et al., 2013).

Additional measures of socioeconomic status (SES) are likely predictors of skin-related and global QOL among women experiencing breast radiodermatitis. In our study, women with a lower income reported more bother by radiodermatitis. This level of bother is currently an unexplored area. However, Wadasadawala et al. (2009) found financial

concerns had a negative impact on global QOL among women receiving whole breast radiotherapy. Nutritional status is an important SES factor in wound healing (Marín Caro, Laviano, & Pichard, 2007). Dietary factors may play a role in skin toxicity with poorer women consuming a less healthy diet. No previous studies exploring this topic where found, therefore research is needed in this area.

Recommendations for Clinical Practice

Caution must be taken when generalizing the results of a small pilot and feasibility study to clinical practice. Still, a number of women in our study who experienced severe radiodermatitis recommended that more emphasis should be placed on teaching about the worst case scenario for skin toxicity. They recommended that photographs of each possible grade of skin toxicity be included in the teaching plan. One participant felt the radiation oncology staff intentionally downplayed how bad radiodermatitis really is. She perceived that all women develop moist desquamation. This suggests that it might be helpful to include the proportion of breast cancer patients expected to develop each grade of radiodermatitis to the teaching plan.

Conclusions

A number of preliminary conclusions can be drawn from our pilot study. Our piloted measures were feasible. We plan to implement minor changes in our next study. We found participant-reported bra cup size and clinician-measured breast length were extremely discordant, an important consideration when using breast size as a predictor of radiodermatitis.

Radiation dermatitis had a significant negative effect on skin-related QOL, but not on global QOL in our study population. The results of our examination of the DLQI when

used for breast radiodermatitis are promising. However, additional larger studies among more diverse populations are needed.

We estimated the face, content, concurrent, construct validity, and reliability of the DLQI among women with breast radiodermatitis in our pilot study. Expert radiation oncology nurses approved the content of the DLQI. Agreement between participant ratings on the DLQI and narrative feedback on each item was good ranging from 71to 98%. The variance for the work and study subscale of the DLQI was zero in our study population and was automatically removed from the principal component analysis (PCA) and Cronbach's alpha. A PCA was implemented to estimate the construct validity of the DLQI. A direct oblimin rotation led to the DLQI subscales loading exclusively on one of two components, indicating that each of the remaining subscales should be retained. The reliability analysis of the remaining DLQI subscales demonstrated good internal consistency with a Cronbach's alpha of $\alpha = .54$. Therefore, the DLQI was deemed satisfactory for use in our study population.

The results of our study that focused on the most important item of the DLQI provide a glimpse into the perceptions of breast cancer patients who receive external radiotherapy in a community setting and experienced radiation dermatitis. Some women expressed that radiodermatitis had profound impact on their quality of life while other were surprised that radiation therapy was easy compared to chemotherapy. Our findings parallel those found in a previous study by Schnur, Ouellette, Dilorenzo, Green, and Montgomery (2011) conducted in an urban setting. Our results provide insight into the thoughts and needs of women undergoing external radiotherapy of the breast. Individual differences must be addressed and care tailored to the unique needs of each woman.

Additional studies focusing specifically on skin-related quality of life are needed.

The results of this study support our original conceptual framework presented in Figure 3.1. We hypothesized that whole breast external radiotherapy, physical characteristics such as skin phototype and breast size, and lifestyle behaviors including smoking and body mass index (BMI) would influence the physical changes that are collectively described as radiodermatitis. We further hypothesized that radiodermatitis would impact skin-related and global QOL. While some variables demonstrated stronger relationships than others, overall, the conceptual framework was congruent with our findings.

Our first next steps include using the data from this study to inform a second pilot study that additionally explores the role of genetic and inflammatory markers on the development of breast radiodermatitis and changes in skin-related QOL. Additionally, we hope to measure light reflectance spectroscopy in the seven areas of the treatment field then compare those measurements against clinician-rated skin toxicity in the same areas. Eventually, we hope to participate in a large international study of breast radiodermatitis using multiple cancer programs. This design would provide sufficient power to accurately detect small but significant changes and afford adequate diversity to produce results that are more widely generalizable. Identifying the steps and moderators of radiodermatitis development may allow the development of effective precision measures to prevent and manage this distressing treatment-induced toxicity.

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Table 8.1

Gene Symbols Associated with Radiodermatitis and their Full Name

Gene Symbol	Full Name	Study First Author & Publication Date
ABCA1	ATP-binding cassette, sub-family A (ABC1), member 1	Isomura, 2008
ATM	ATM serine/threonine kinase	Ho, 2006
GSTP1	glutathione S-transferase pi 1	Ambrosone, 2006
IL12RB1	interleukin-12 receptor	Isomura, 2008
MC1R	melanocortin 1 receptor (alpha melanocyte stimulating hormone receptor)	Latreille, 2009
NOS3 (eNOS)	nitric oxide synthase 3 (endothelial cell)	Terazzino, 2012
RAD21 (hHR21)	RAD21 cohesin complex component	Ho, 2006
SOD2	superoxide dismutase 2, mitochondrial	Ho, 2006
TGBF1	transforming growth factor, beta 1	Anscher2010; Ho, 2006
XRCC1	X-ray repair complementing defective repair in Chinese hamster cells 1 (*Homo sapiens*)	Ho, 2006; Terazzino, 2012
XRCC3	X-ray repair complementing defective repair in Chinese hamster cells 3 (*Homo sapiens*)	Ho, 2006; Werbrouck, 2009
XRCC6 (Ku70)	X-ray repair complementing defective repair in Chinese hamster cells 6 (*Homo sapiens*)	Werbrouck, 2009

Table 8.2

Inflammatory Markers Associated with Radiodermatitis

	Full Name	**First Author & Publication Date**
CCL2	chemokine (C-C motif) ligand 2 GENE	Muller, 2011
CCL4	chemokine (C-C motif) ligand 4	Muller, 2011
CXCL12	chemokine (C-X-C motif) ligand 12	Muller, 2011
IL-1a	IL1A interleukin 1, alpha	Zhou, 2001
IL-1b	IL1B interleukin 1, beta	Zhou, 2001
IL-6	IL6 interleukin 6	Zhou, 2001
TGFß	Transforming growth factor beta	Okunieff, 2006; Xiao, 2006; Muller, 2007; Anscher, 2010
TNFα	Tumor necrosis factor alpha	Nawroth, 2011

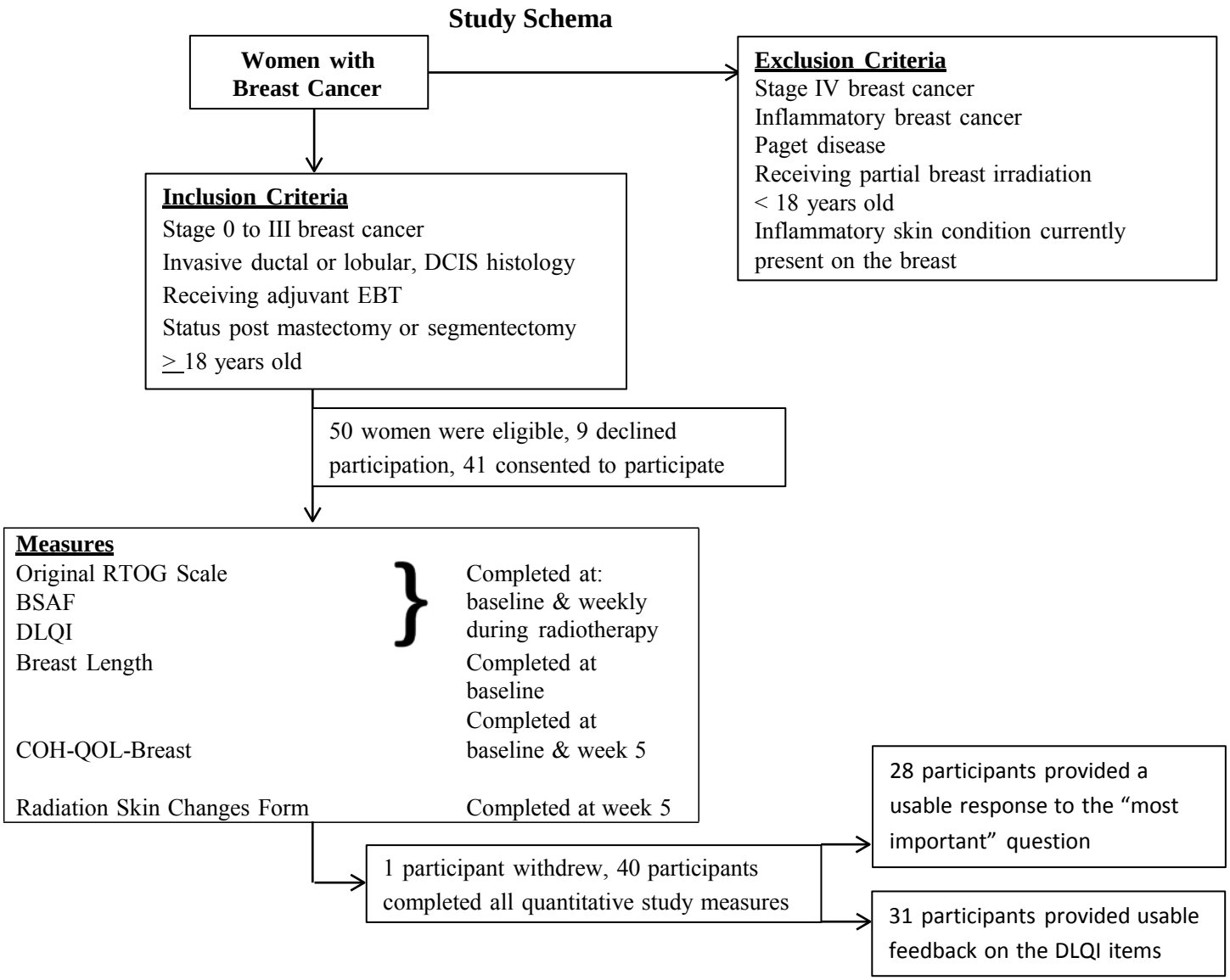

Figure 8.1 Final schema for study

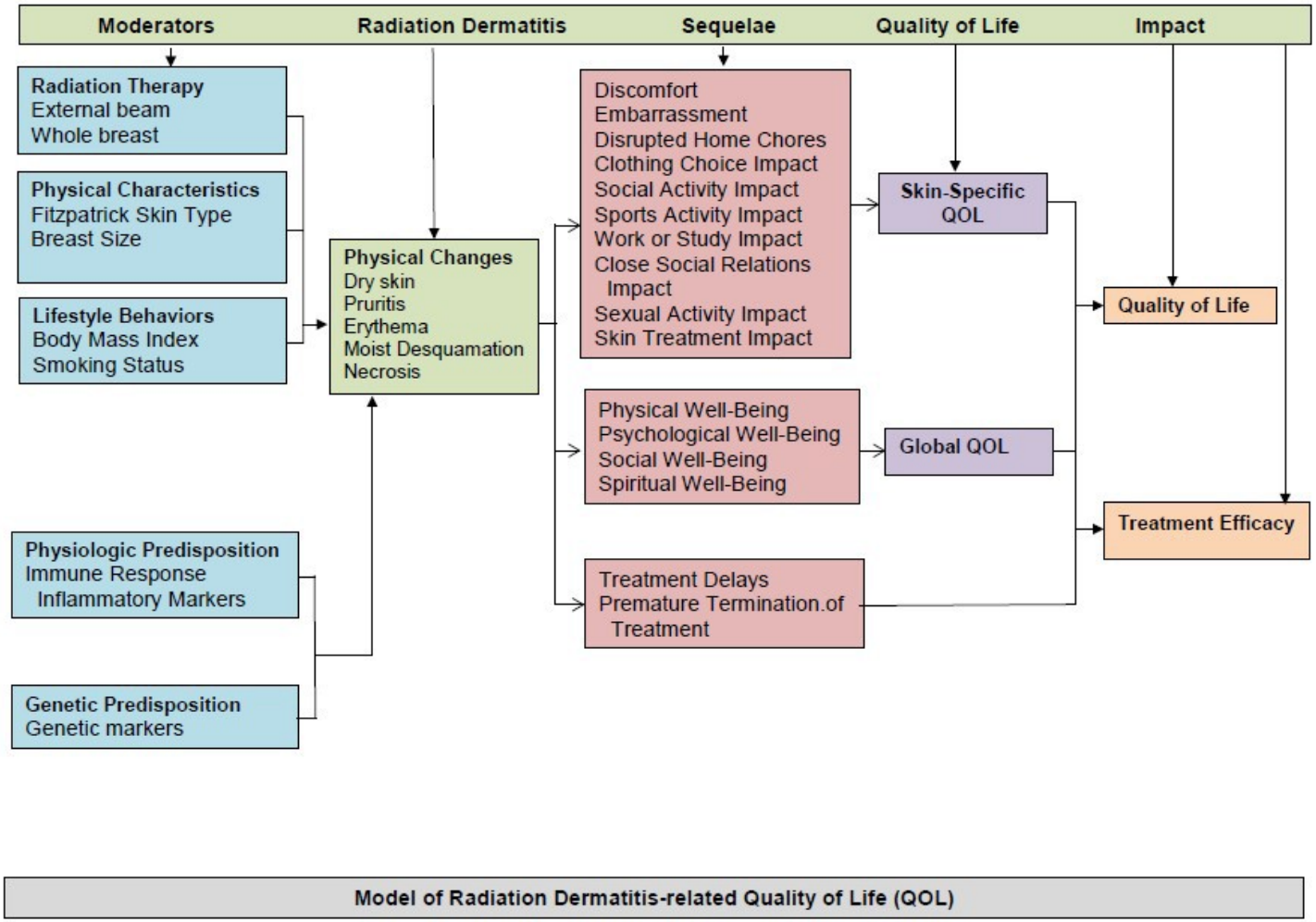

Figure 8.2. Logic model of radiation dermatitis-related quality of life (future study)